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VOLUME 97(1), JAN-FEB 1988

ANNALS

OF OTOLOGY, RHINOLOGY & LARYNGOLOGY

ANNALS OF HEAD & NECK MEDICINE & SURGERY

⑧

Papers from the American Otological Society, Inc, meeting, including

Hearing Preservation in Unilateral Acoustic Neuroma Surgery

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Cholesteatoma Surgery: Canal Wall Down Procedures

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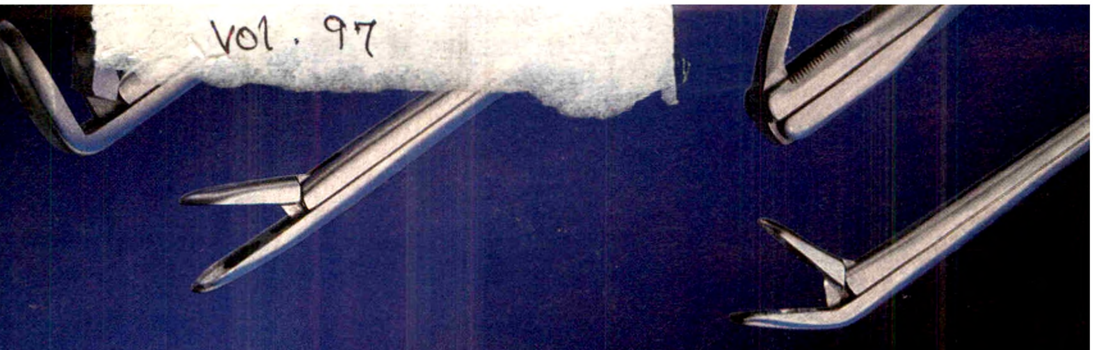
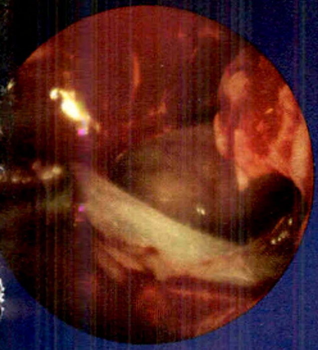
Karl Storz: The revolution in endoscopic sinus surgery continues.

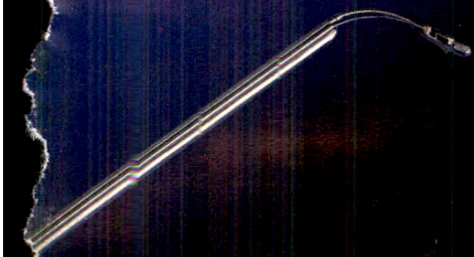
Viewed with a 30° telescope in the right nasal cavity, we see mucopurulant drainage from the middle meatus into the nasopharynx. Note the accessory maxillary ostium in the area of the fontanelle.

Vol. 97



Following ethmoidectomy and middle meatal antrostomy, thick mucous is aspirated from the left maxillary sinus as seen through a 30° telescope.





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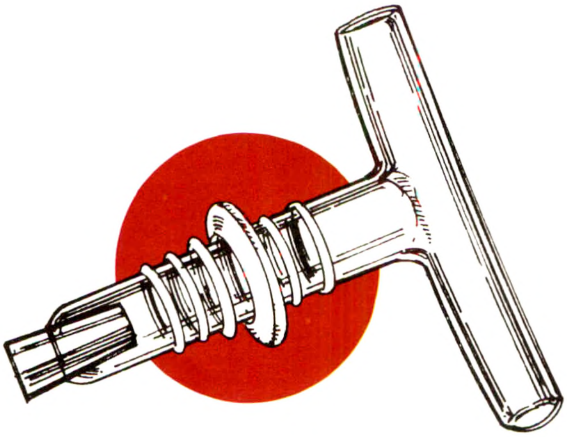

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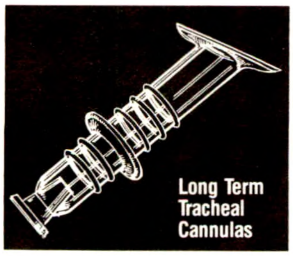

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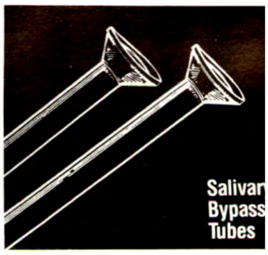

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VOLUME 97 JANUARY-FEBRUARY 1988 NUMBER 1

CONTENTS

Papers Presented at the Meeting of the American Otological Society, Inc

Recent Advances in Cochlear Blood Flow Measurements
Jonathon S. Sillman, MD; Michael J. LaRouere, MD; Alfred L. Nuttall, PhD; Merle Lawrence, PhD; Josef M. Miller, PhD 1

Cochlea and Heart as End-Organs in Small Vessel Disease
James D. Sidman, MD; Jiri Prazma, MD, PhD; Stephen H. Pulver; Harold C. Pillsbury III, MD 9

Multiple Otopathologic Disorders
Michael M. Paparella, MD; Patricia A. Schachern; Marcos V. Goycoolea, MD, PhD 14

Diagnosis of Retrocochlear and Central Vestibular Disease by Magnetic Resonance Imaging
Galdino E. Valvassori, MD 19

Cholesteatoma in the Pediatric Age Group
David R. Edelstein, MD; Simon C. Parisier, MD; Gurpreet S. Ahuja, MD; Charles Juarbe, MD; Patricia Chute, MA; Shula Wenig, MS; Steven M. Kaye, PhD 23

Cholesteatoma Surgery: Canal Wall Down Procedures
James L. Sheehy, MD 30

Potentiation of Ototoxicity by Glutathione Depletion
Douglas W. Hoffman, PhD; Craig A. Whitworth; Kitty L. Jones-King; Leonard P. Rybak, MD, PhD 36

Ultrastructural Changes in Vestibulo-ocular Neurons Following Vestibular Neurectomy in the Cat
Richard R. Gacek, MD; Michael J. Lyon, PhD; Joanne Schoonmaker 42

Neurons of the Inferior Medullary Velum in the Cerebellopontine Angle
Leonid I. Terr, PhD; William F. House, MD 52

Hearing Preservation in Unilateral Acoustic Neuroma Surgery
Gale Gardner, MD; Jon H. Robertson, MD 55

Morphologic Effects of Glycerol and Urea on Cochlear Tissues of the Chinchilla
Charles G. Wright, PhD; David H. Lee, MS; William L. Meyerhoff, MD, PhD; Peter S. Roland, MD 67

Eliminating the Toynbee Phenomenon in Patients With Nasal Packs
Yehuda Finkelstein, MD; Yuval Zohar, MD; Nelu Laurian, MD 74

Cochlear Hair Cell Loss in Ears With Cholesteatomas. Scanning Electron Microscopy Study
Richard A. Chole, MD, PhD; Maggie Chiu, MS 78

Spinal Accessory Nerve Function Following Neck Dissection
Francesco Zibordi, MD; Federico Baiocco, MD; Cristina Bascelli, MD; Artilio Bini, MD; Alfredo Canepa, MD 83

Stapedial Electromyograms Recorded by Electrocochleography
Nobuya Yagi, MD; Hiroaki Nakatani, MD 87

X-Ray Study of the Month. Cerebrospinal Fluid Serous Otitis Media
Ilana Seligman, MD; Rodney P. Lusk, MD 92

Pathology Consultation. Sialadenosis
John G. Batsakis, MD 94

Letters to the Editor . . . 96

Book Reviews . . . 96

Preliminary Programs — 1988
- American Society of Pediatric Otolaryngology . . . 99
- Combined Otolaryngological Spring Meetings
  - American Neurotology Society . . . 100
  - American Otological Society, Inc . . . 101
  - American Laryngological Association . . . 101
  - American Broncho-Esophagological Association . . . 102
  - American Laryngological, Rhinological and Otological Society, Inc . . . 103

Instructions to Authors . . . 15a

Index to Advertisers . . . 16a

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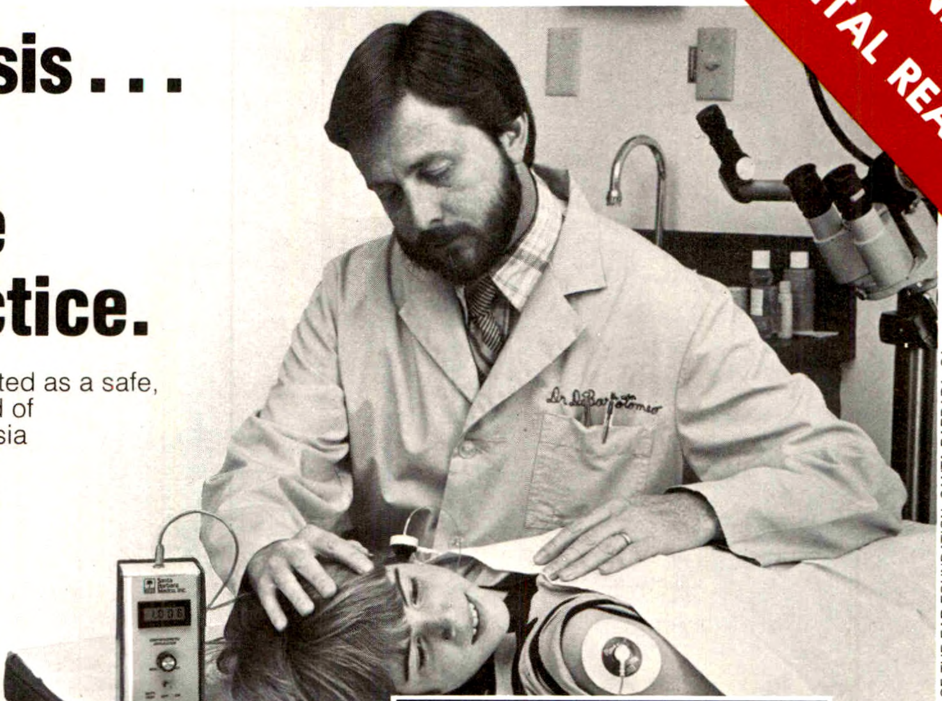

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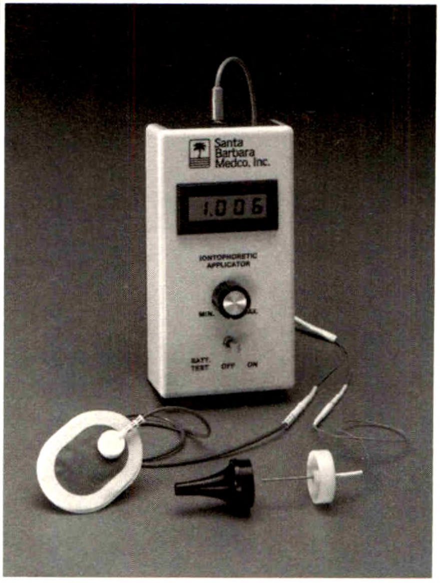

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1. Echols, D., Norris, and H. Tabb. "Anesthesia of the Ear by Iontophoresis of Lidocaine." Arch. Otolaryngology, 101, 1975, 418-421.
2. Comeau, M., and R. Brummett. "Anesthesia of the Human Tympanic Membrane by Iontophoresis of a Local Anesthetic." Laryngoscope, 88, 1978, 277-285.

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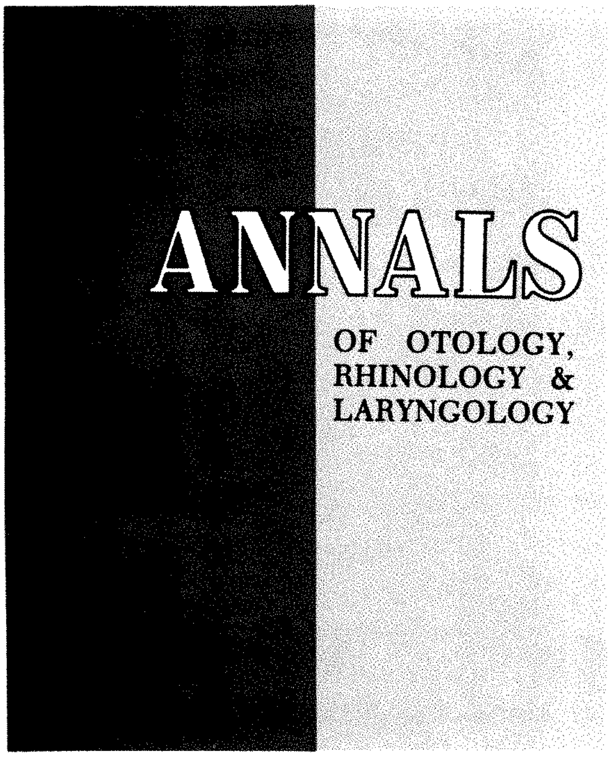

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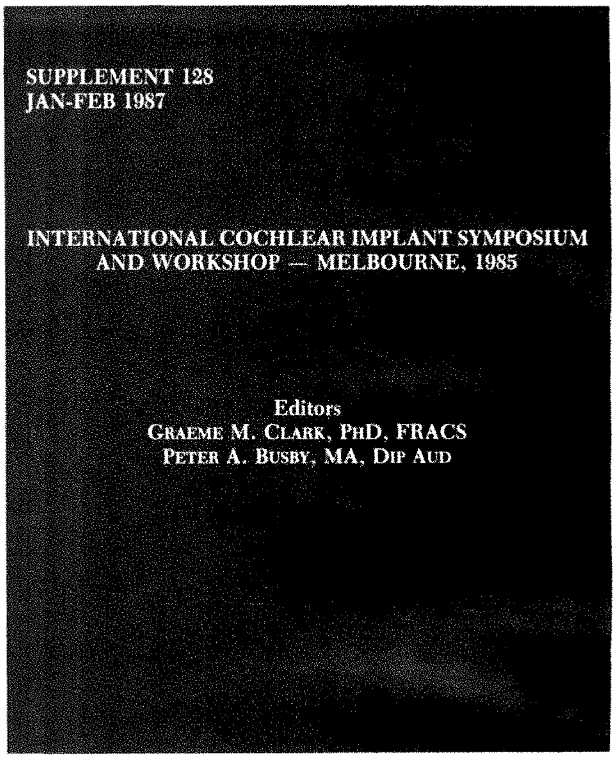

SUPPLEMENT 128
JAN-FEB 1987

INTERNATIONAL COCHLEAR IMPLANT SYMPOSIUM
AND WORKSHOP — MELBOURNE, 1985

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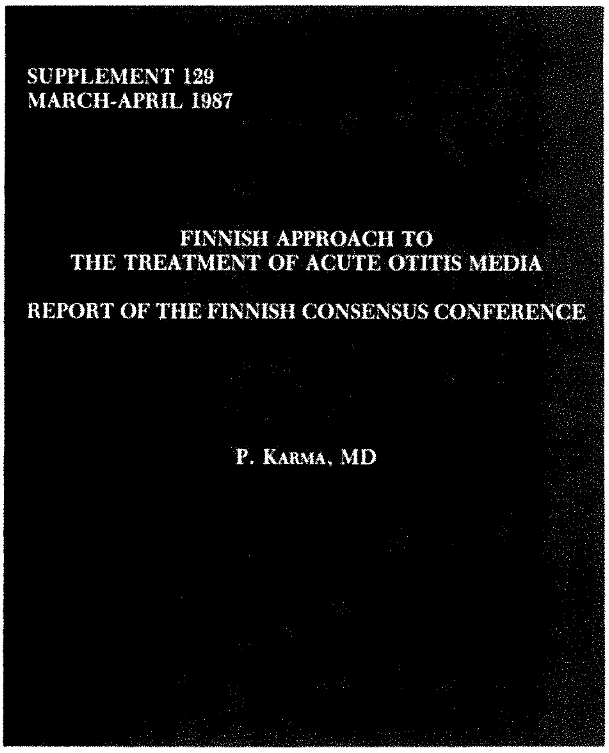

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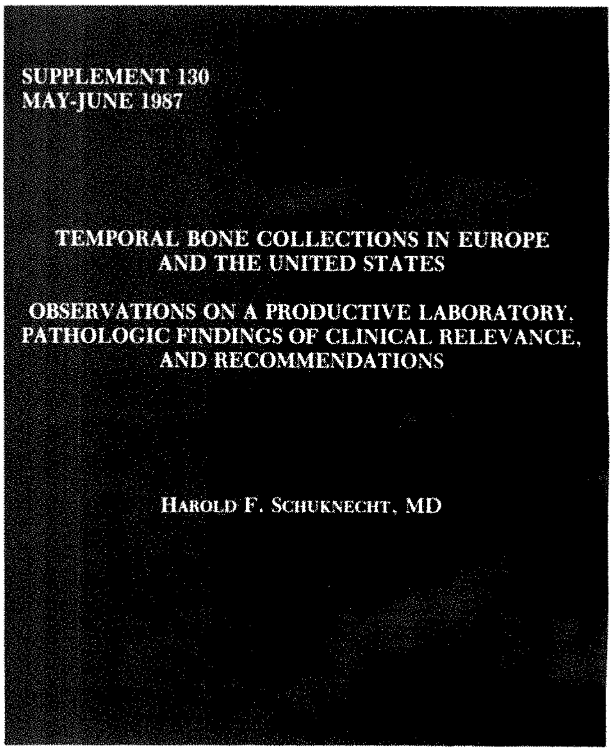

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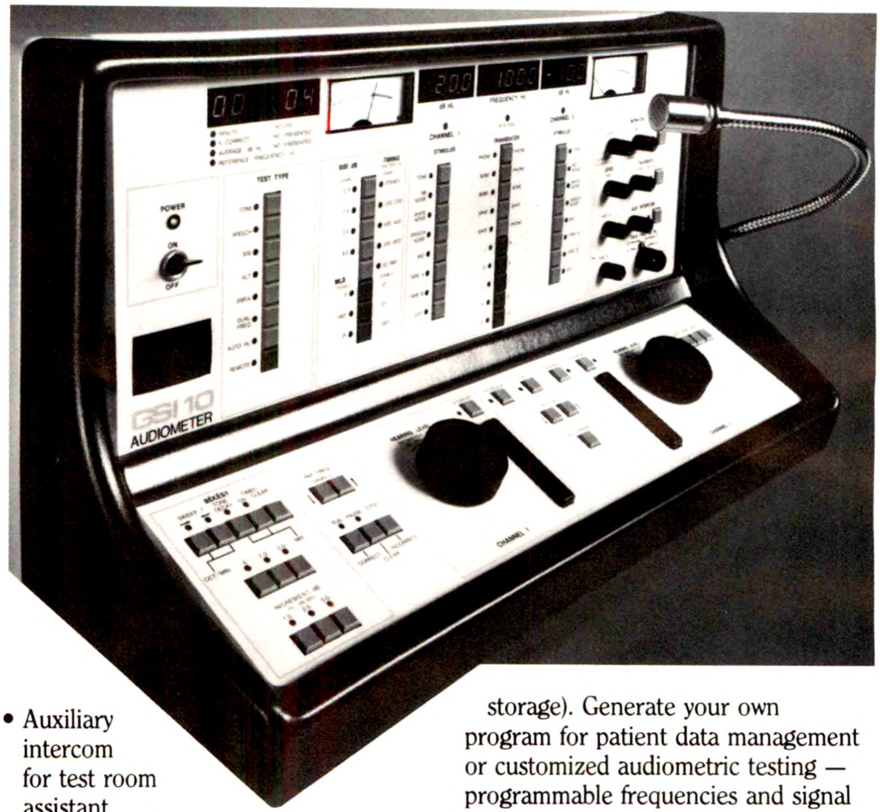

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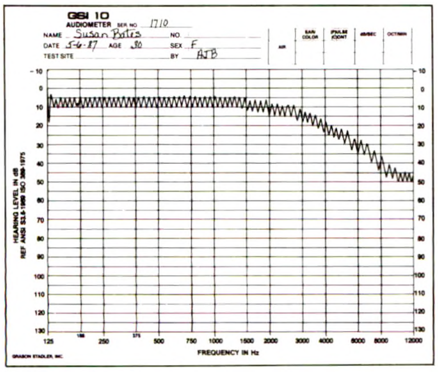

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RECENT ADVANCES IN COCHLEAR BLOOD FLOW MEASUREMENTS

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ANN ARBOR, MICHIGAN

Changes in blood flow to the inner ear have been thought to influence or underlie a number of cochlear diseases, including some forms of noise-induced hearing loss, sudden hearing loss, and Meniere's disease. Recently, important advances have been made in two technologies for the study of cochlear blood flow. The first is in the area of vital microscopic studies of cochlear microcirculation, and the second is based on the introduction of laser technology in the form of laser Doppler flowmetry. In this report, measurements are given of changes in cochlear circulation caused by carbon dioxide breathing, intravenous phenylephrine injection, systemic hemodilution, positive end expiratory pressure, and direct electrical stimulation of the cochlea. From these changes, we observe that cochlear blood circulation responds to systemic blood pressure alterations and is subject to local flow control mechanisms. Linearity and speed of response of the laser Doppler instrumentation also are shown. These advances show promise for contributing to our knowledge of control mechanisms of inner ear blood flow and for revealing the influence of various pharmacologic agents of potential clinical value.

KEY WORDS — blood flow measurement, cochlear microcirculation, intravital microscopy, laser Doppler flowmetry.

INTRODUCTION

The study of cochlear microcirculation has a long history, motivated by the supposition that it plays an important role in maintaining the normal homeostatic environment of the inner ear and by the assumption that certain otologic disorders have vascular causes. It is presumed that these disorders may be improved by increasing blood flow to the inner ear with various vasoactive agents.

From studies of inner ear anatomy, physiology, and biochemistry, we know the activity of this structure to be demanding and its metabolic rate high. Its exquisite sensitivity to oxygen depletion and metabolic inhibitory drugs, its uptake of 2-deoxyglucose, and its disproportionately large and intricate vascular supply all support the concept that a stable blood flow to the inner ear is of major importance for its normal function. Histologic evidence has indicated that changes in the vascular system of the cochlea may underlie certain disorders, perhaps reflecting a compromised metabolism. These include components of presbycusis,[1] Meniere's disease,[2,3] and noise-induced hearing loss.[4-7] Of greatest recent interest has been the concept of a vascular cause for certain forms of sudden hearing loss.[8-10] However, this is a concept of exclusion, since it is based primarily on the absence of data to support alternative causes.

For the most part, these views are based upon either indirect data or general physiologic principles. This in turn reflects the difficulty of direct measurement and evaluation of blood flow in the inner ear. Despite the absence of direct supporting data, presumed vascular disorders of the inner ear have been treated with drugs, the choice of which is based upon their effectiveness as systemic cardiovascular agents.[11-13] There is a clear need for greater understanding of the mechanisms controlling cochlear blood flow (CBF) and the role of microcirculatory changes in otologic disease. To achieve this end, the first step has been to devise better methods for measuring CBF. The difficulty of performing direct, quantitative, and dynamic measures of CBF has been described in a number of recent publications.[14-16] Of the techniques employed to date, each has it drawbacks. However, it may be that with recent developments and with a combination of procedures, we will now be able to evaluate appropriately the normal state and pathophysiologic changes in CBF.

The first direct observations of CBF used intravital microscopy (IVM).[17,18] This technique allows visualization of the major vascular beds of the lateral wall and the basilar membrane[19] in the living animal. Changes in blood flow pattern, flow rate, and vessel lumen diameter can be assessed under resting conditions and with experimental manipulation. In contrast to the histologic studies of the cochlea that preceded this technology, IVM offers a direct and dynamic measure of blood flow, based upon observation of RBC and plasma motion and factors that influence flow (ie, vessel lumen diameter). It is uncontaminated by possible changes associated with death of the animal and histologic preparation. It is, however, not without restric-

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From the Kresge Hearing Research Institute, University of Michigan Medical Center, Ann Arbor. This work was supported in part by the National Institutes of Health/Public Health Service Studies of the Cochlear Prostheses grant NS 21440, Control of Inner Ear Microcirculation grant NS 11731, and grants from the Deafness Research Foundation and American Otological Society, Inc.

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REPRINTS — Josef M. Miller, PhD, Kresge Hearing Research Institute, 1301 E Ann St, Ann Arbor, MI 48109-0506.

tions. The technique requires the removal of otic capsule bone over the lateral wall vessels to permit their direct visualization. Under the best of conditions this is a rather invasive procedure. However, with careful exposure of the membranous cochlear labyrinth, CBF appears unaffected as measured by other techniques. When the technique is applied to the basilar membrane vessels, fluid compartments and some vessels must be compromised. Quantification of vascular parameters is difficult, and the field of view is quite restricted. This restricted view, however, represents a strength of the method, since it results in great specificity of measurement, which has been demonstrated to be of particular advantage.[14]

Microsphere measurements of CBF were introduced in the late 1970s by Angelborg et al.[20] This measure is a "gold standard" of circulatory physiology. Based on an assessment of the number of trapped spheres in the capillary beds of the inner ear following an intracardiac bolus injection of a known quantity of spheres and the acquisition of a reference blood sample, the microsphere technique permits a quantitative measurement of CBF. When combined with a soft surface histologic preparation[5] allowing an assessment of the distribution of trapped microspheres, the evaluation of regional as well as whole organ flow is possible.[21,22] Its restrictions are that it is a static measure allowing only one or two measurements within a short (eg, 30 minute) period of time. Also, given the small cochlear blood volume, an enormous number of microspheres must be injected systemically to ensure trapping of an adequate sample in the cochlea; this injection taxes the normal physiology of the animal. There is also the possibility that trapped microspheres may alter the overall flow pattern in a vascular bed, thus influencing measurements that reflect changes of CBF over a period of time.

Laser Doppler (LD) flowmetry, the most recently introduced method for CBF study,[23] has been shown to provide a dynamic measure of CBF. The general characteristic of this measure and the operating principles of this device have been described elsewhere.[24] It provides a voltage output that is proportional to the number and velocity of RBCs in a measurement volume, ie, flux. Its advantages are that the equipment is commercially available, it is a relatively noninvasive procedure, and it provides a real-time assessment of CBF. From studies in skin it has been shown to provide a linear measure of blood flow. Its disadvantages are that while we know the measurement volume is restricted to the cochlea, we cannot specify the vessels contained in that measurement volume, and while the measure is linear, we cannot provide a physical reference for the output in order to calibrate the instrument adequately.

In addition to these direct measures of CBF, a number of indirect measures related to CBF also have been applied. These include measurement of oxygen tension in the fluids and tissues of the inner ear in animals[7,25-28] and humans,[11,28,29] perilymph production,[30] and hydrogen clearance.[27] These measures may each complement direct CBF measures to provide a more comprehensive view of inner ear function.

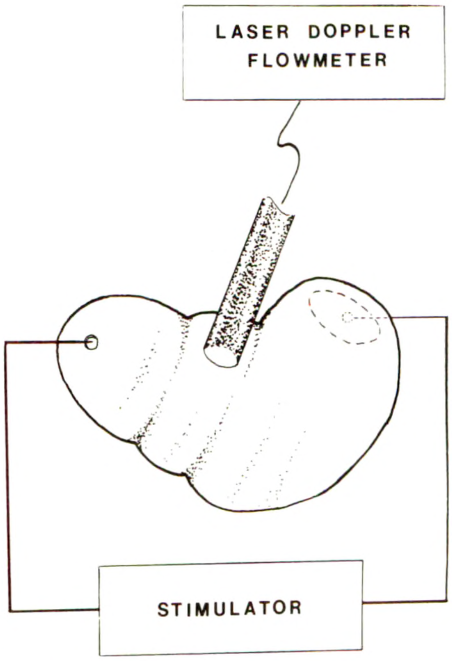

Fig 1. Schematic drawing of experimental arrangement for measuring effect of electrical stimulation on cochlear blood flow with laser Doppler system. Current is passed differentially between electrodes from apex to round window. Laser Doppler probe is placed perpendicular to otic capsule, overlying strial band, typically on first or second turn.

The purpose of this investigation was to assess the current status of development of IVM and LD technologies for measuring CBF and to examine their response to direct manipulation of inner ear flow. Our intention was to define some of the characteristics of each technique and of CBF that may limit the application and restrict the interpretation of these methods, to identify their strengths and weaknesses, and to determine if each provides complementary or identical information on CBF.

METHODS

Animals and Preparation. Young albino and pigmented guinea pigs (250 to 450 g) were used in this investigation. The middle ear of each animal was assessed directly, and only those observed free from infection were used. Each animal was anesthetized with diazepam (5 mg/kg intraperitoneally) and fentanyl (0.32 mg/kg intramuscularly). They were tracheotomized. The carotid artery was cannulated for blood pressure monitoring in all animals, and the jugular vein was cannulated for those in which drugs were administered. Animals were

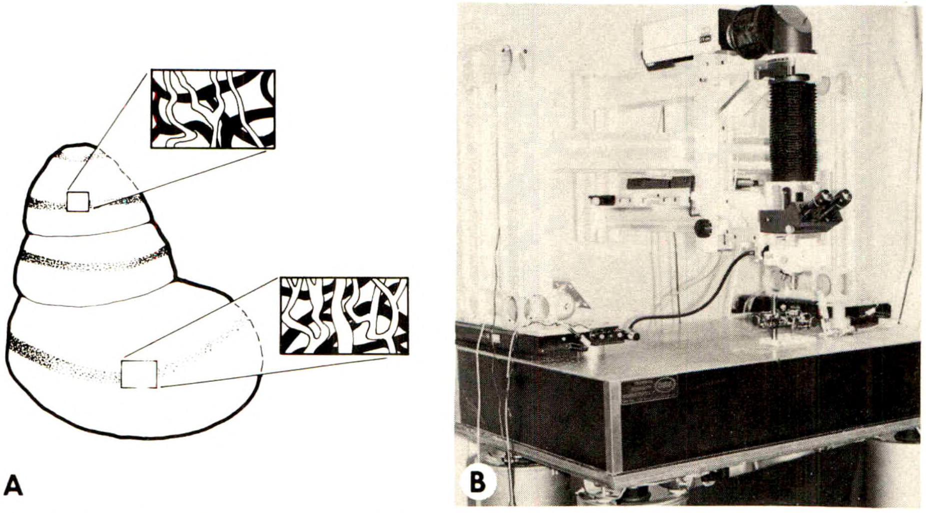

Fig 2. Intravital microscopy. A) Placement of fenestras for viewing lateral wall vasculature of first and third turns, and expanded views of vessels observed. B) Vital microscopy equipment. Light is directed vertically from microscope to video camera, both of which are mounted on electrically driven movable frame. Experimental preparation and measurement equipment are placed on vibration-free hydraulic platform.

placed in a head restraint with a heating element to maintain the temperature of the otic capsule within physiologic limits regardless of middle ear exposure. In addition, each animal was wrapped in a heating pad with a feedback system to maintain normal core temperature. Finally, for some animals in which curare was administered (0.3 mg intramuscularly to control muscle contractions during application of high levels of electric current to the cochlea), the animals were respirated and expired carbon dioxide was monitored and maintained within normal limits.

For LD and IVM studies, the bulla was opened widely using a ventral approach to expose the cochlea. In 15 animals, 0.2 mm platinum-iridium ball electrodes were placed, with the aid of a micromanipulator, on the round window and in a small opening at the apex of the cochlea. As illustrated in Fig 1, LD measurements typically were taken at the level of the second turn, although on occasion measurements were taken from other sites on the cochlea.

In the case of IVM-studied animals, a small fenestra was created at a selected site over the spiral ligament. Comparative measurements were taken from individual animals at basal and third turn sites (Fig 2A). To create these windows, a rectangle is scored, carefully and repeatedly, in the bone over the selected site, until it is possible to lift the bone from the lateral wall, exposing the underlying vessels. The window typically can include those vessels from the terminal endings of the radiating arterioles through the initial segments of the collecting venules.

Intravital Microscopy and Laser Doppler Technology. The main characteristics and principles that underlie IVM and LD technology have been described elsewhere.[14,15,17,18,23,24,31-35] Briefly, IVM, based upon a direct visualization of the vessel bed to be studied, can be a bright field or a fluorescence technique. The degree to which an adequate assessment of CBF can be made will depend upon the stability of the preparation, the ability to maintain a normal condition about the exposed vasculature, the optics of the microscope system, and the image recording, enhancement, and analysis techniques. Each of these requires careful consideration in applying this technology.[14] The system used in this investigation is illustrated in Fig 2B. It consists of an optical compound microscope modified for fluorescent-type microscopy, attached to a movable carriage on a vibration isolation table.

Almost all early IVM of CBF was done with bright field microscopy. Although many important observations can be made using bright field techniques, certain improvements are garnered by fluorescence methods. Two advantages are 1) improved contrast of blood vessels and flowing cells in thick tissue preparations such as the spiral ligament and 2) the ability to quantify the vessel lumen because fluorescent plasma extends directly to the endothelial cell wall. The essential components of the intravital microscope are a lens with a long working distance objective (10 mm is sufficient for the guinea pig) and a recording system to permit off-line analysis of vascular components. Cinematographic methods previously were favored, and they have given way to video technology.[14,36,37]

For fluorescence microscopy, the illumination pathway can be provided directly onto the cochlea from an appropriate lamp using fiberoptic light guides, or through the microscope by vertical illumination techniques. The vertical illumination technique has the advantage of limiting stray light, which decreases image contrast. With vertical illumination, only a small area under the lens is illuminated. Appropriate filters (chosen according to the fluorochrome) are placed in the optical path to reveal the fluorescence and to eliminate incident excitation light.

The LD measurement systems (TSI-Laserflow blood perfusion monitor 403, TSI Corp, St Paul,

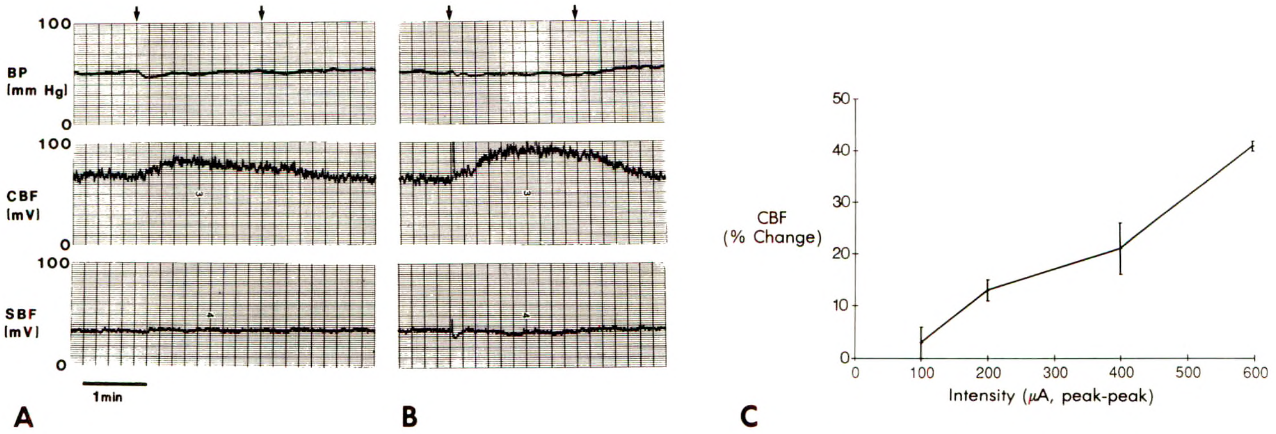

Fig 3. Laser Doppler–measured responses of cochlear blood flow (CBF) to electrical stimulation. Recordings at A) 400 μA and B) 600 μA (peak-peak) from same animal. Arrowheads indicate onset and offset of current (duration of 2 minutes). Skin blood flow (SBF) and blood pressure (BP) traces are shown. Numbers in center of chart paper indicate channel numbers. C) Characteristic input-output function taken from one animal. Each point represents mean of ten stimulations at given intensity. Error bars represent one standard deviation.

Minn; Periflux laser Doppler flowmeter, Perimed AB, Stockholm; MEDPACIFIC LD 5000, MEDPACIFIC Corp, Seattle) are based on the detection of spectrally shifted backscattered laser light, caused by RBCs moving through a defined measurement volume. For skin, this volume is 1 mm^3.[24] Helium-neon laser light is transmitted via a fiberoptic light guide to a measurement probe, which can be less than 1 mm in diameter (including the receiving light guide). The amount of frequency-shifted, reflected light depends upon the number of RBCs in the measurement volume, their velocity relative to the LD probe, the distance of the RBCs from the probe, and backscattering among other reflective tissues. This weighted (normalized) Doppler-shifted light is analyzed and converted to a voltage. In one instrument (MEDPACIFIC 5000), a DC component signal output also is provided, having characteristics related to the amount of blood in the measurement volume. In other instruments (TSI and Periflux Pf2 and Pf3), an attempt has been made to provide components of the reflected signal that may depend on velocity, flux, and volume of RBCs measured. The testing and quantification of these features for measurements in the cochlea are still to be performed.

Experimental Manipulations. Agents selected for the purposes of the study included systemically administered phenylephrine, 10% CO_2 in air, direct electrical stimulation of the cochlea, manipulation of positive end expiratory pressure (PEEP), and hemodilution. Phenylephrine is a potent alpha-agonist causing diffuse systemic vasoconstriction, although its direct effect on cochlear circulation is less well understood.[32,38] A bolus injection of phenylephrine provides a rapid and transient change in CBF that parallels changes in systemic blood pressure. Carbon dioxide yields a gradual and maintained increase in CBF. Changes in CBF associated with direct electrical stimulation of the cochlea reflect a locally initiated mechanism.[39] Positive end expiratory pressure is a manipulation for reducing cardiac output and permits controlled reduction in systemic blood pressure. Hemodilution (normovolemic) causes a rheologic change independent of blood pressure. Reduction in the number of RBCs results in a reduction of blood viscosity. Tissue oxygen needs are still met if the hematocrit reduction is not great and the reduced viscosity leads to an increased velocity of blood flow in all organs of the body.

Both LD and IVM measurements were made of the effects of electrical stimulation. Primary observations were made using 500-Hz continuous sinusoidal stimulation at various intensities. This frequency has been shown to be the most effective frequency for eliciting a CBF response.[39] Stimulation was delivered for a 2-minute period, and the response measured was the change from baseline flow observed during the second minute of stimulation. Measurements were normalized relative to systemic blood pressure to eliminate transient systemic influences. The LD measure was the voltage output of the flow component of the TSI. For IVM, the measure was based upon the assessment of changes in the velocity of labeled RBCs through a selected vessel of the stria vascularis.[14] For any given IVM observation, the measurements were repeated on a number of lateral wall vessels, and a mean response is presented. Observations of changes in vessel diameter with some manipulations also have been made.[40]

The effects of continuous (0.1 mL/min) and bolus (0.0025 mg/kg and 0.0075 mg/kg) intravenous injection of phenylephrine were studied with both LD and IVM measurements. The measurement was made at the peak of the response for bolus injections and when the blood pressure response had stabilized at its new value for continuous injections. For IVM assessment of CO_2 and PEEP, measurements were made 3 to 5 minutes after initiation of the ma-

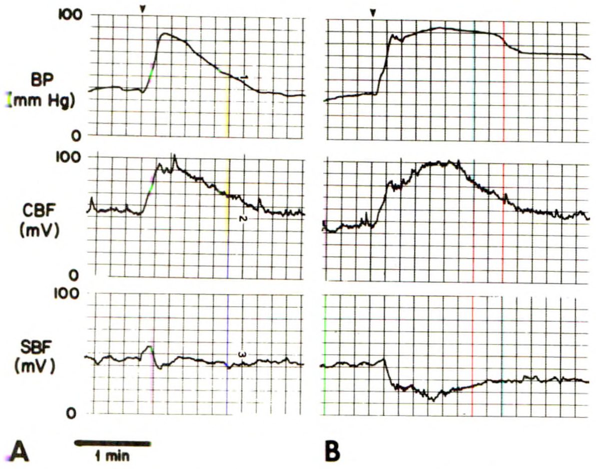

Fig 4. Response of cochlear blood flow (CBF), blood pressure (BP), and skin blood flow (SBF) to bolus injections of A) 0.0025 mg/kg and B) 0.0075 mg/kg phenylephrine. SBF declines, while CBF and BP increase rapidly. These effects are greater and of longer duration with higher dose. At higher dose, CBF recovers sooner than BP, perhaps reflecting autoregulation (see text). Numbers in center of chart paper indicate channel numbers.

nipulation, when the response had stabilized. For observations on PEEP, a blood pressure change was maintained constant over the period of study by varying resistance at the expiratory cannula.

RESULTS

Laser Doppler Flowmetry. Figure 3A,B shows a characteristic response of the LD flowmeter to direct electrical stimulation at 500 Hz. The electrical stimulation was delivered at 400 and 600 μA (peak-peak). These intensities represent a moderate and a high value of stimulation within the dynamic range of CBF response changes observed with this stimulus (Fig 3C). With higher intensities (800 to 1,000 μA), systemic blood pressure changes have been observed in these preparations, but not at the levels shown here. The CBF rises in a gradual fashion during the first 30 to 40 seconds following onset of the stimulation and then is maintained until the stimulus is terminated. There is occasionally a small initial overshoot in the rise of the CBF response, but by 1 minute it is stable. We have observed it to remain stable for periods of stimulation greater than 10 minutes. The lack of a systematic change in blood pressure indicates that this is a locally mediated effect on CBF, and control studies indicate that it is not the result of a movement or electrical or equipment artifact (J. S. Sillman et al, unpublished data).

Figure 3C is a representative input-output function of the LD-measured CBF response to electrical stimulation from threshold levels to an intensity below that eliciting a systemic blood pressure response. The response appears to be a linear function of stimulus intensity, with an extrapolated threshold on the order of less than 100 μA.

Figure 4 shows the LD-measured response to phenylephrine administered as an intravenous bolus in two doses. Phenylephrine causes a contraction of peripheral arterioles. Systemic blood pressure increases and CBF follows the transient changes in blood pressure, particularly at lower dose levels. At the higher dose levels, an elevated blood pressure level is maintained while CBF begins to recover. For the higher dose level, blood pressure and CBF changed at a rate of 12.4% and 8.7% of their respective resting values per second. This illustrates the ability of the LD flowmeter to follow rapid changes in blood flow. It is noteworthy that with other manipulations, eg, compression of the thoracic aorta, even higher rates of change may be registered with this device.

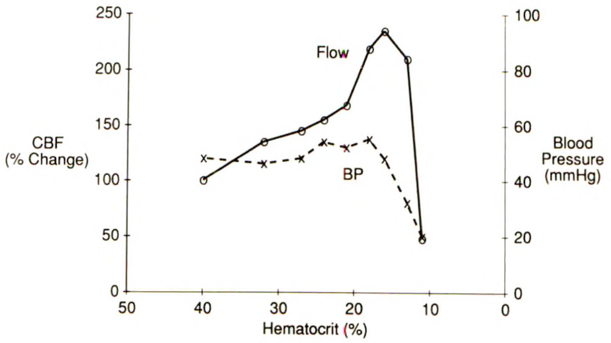

Fig 5. Plot of blood pressure and laser Doppler–measured cochlear blood flow (CBF) as functions of hematocrit. With hemodilution from hematocrit of 40% to 20%, CBF rises while BP remains steady. Below 20% hematocrit, general hypoxia results, with resultant decline in both blood pressure and CBF.

Figure 5 shows the results of normovolemic hemodilution with dextran 75 on the systemic blood pressure and the LD flow measurements. As hematocrit is reduced from the normal value of 40% to about 20% in the typical guinea pig, there is a significant increase in CBF. The flow increase occurs despite no significant change in blood pressure. This illustrates the potential gain in perfusion of tissue that is the result of decreased blood viscosity. Below 20% hematocrit, critical levels are reached, at which significant compromise of oxygen transport capacity occurs. There is a collapse of the systemic physiology, with resulting blood pressure and CBF decrease.

Intravital Microscopy. The speed of individual RBCs is timed electronically from a sensor that operates on a video image of a capillary bed. Normally more than 20 RBCs are evaluated to obtain the average velocity of the vessel flow. Several vessels in the image are averaged to obtain an overall velocity measurement in the Table. The Table shows that phenylephrine given as a continuous intravenous infusion caused a +87.4% increase in CBF as measured by IVM. However, the percentage increase in velocity can be accounted for entirely by the concomitant increase (88.1%) in BP. This situation is moderately different from that observed with an animal breathing 10% CO_2.

CHANGE FROM AVERAGE BASELINE OF COCHLEAR BLOOD FLOW

	Phenylephrine Injection	*10% CO_2 Breathing*	*Local Electrical Stimulation**	*Positive End Expiratory Pressure*
Systemic blood pressure	+88.1%	+15.5%	0	−52.7%
Cochlear blood flow†	+87.4%	+76.8%	+56.3%	−36.5%
No. animals	17	9	4	13

*500 Hz, 400 μA.

†Red blood cell velocity as measured by intravital microscopy.

Although CO_2 breathing resulted in a systemic blood pressure increase of 15.5%, the cochlear RBC velocity was more significantly affected (+76.8%). Local electrical stimulation represents a further level of divergence of the cochlear RBC velocity from systemic factors. It produced a large increase in velocity (+56.3%) with no change in systemic blood pressure. This local response occurred for naturally breathing guinea pigs not given curare. Positive end expiratory pressure causes a decreased blood pressure due to decreased cardiac output. The Table shows that the cochlear RBC velocity also is reduced by PEEP. However, the 52.7% decrease in blood pressure caused by PEEP reduced RBC velocity by only 36.5% in an average taken over a 5-minute period.

DISCUSSION

In regard to current technology for the evaluation of CBF, it is clear that there have been a number of dramatic improvements in the approaches that are now available. Microsphere measures (not reported here), while static and very sensitive to preparation conditions, have provided a precise and quantitative physical determination that may yield information on differential characteristics of regional flow. Current work by Angelborg et al[41,42] using colored microspheres may be a significant development for this technique. In future investigations, the microsphere method, in combination with other quantitative measures of flow, (ie, IVM and hydrogen clearance) may provide a basis for calibration of the LD flowmeter. With such calibration, the ease of interpreting data from the LD flowmeter and its application to clinical problems will be greatly enhanced.

It should be noted that the most recent approach to measuring CBF is the use of radioactive antipyrine injection with subsequent autoradiographic analysis of cochlear tissues.[43] This method relies upon the Fick principle (described by Reivich et al[44]) and thereby gives a quantitative measure of CBF. The advantages of antipyrine injection are that, unlike microspheres, this agent is freely diffusible and therefore does not alter the blood flow itself. Furthermore, using a radioactive molecule instead of a macroscopic particle allows a relatively large sample of tracer to accumulate in the cochlea and thereby avoids the potential sampling error inherent in the microsphere technique. The disadvantage of the antipyrine technique is that it allows only a single static measurement of flow.

Now readily quantified, the IVM provides a measure of RBC velocity and vessel diameter in specific vessels of the lateral wall. It cannot provide information, at this time, on flow in the vessels of the modiolus, and techniques must be developed to permit on-line, real-time assessment of transient changes in vascular parameters. The data presented in the Table indicate that a wide variation in RBC velocity within the cochlear circulation is possible, and that the velocity varies with the type of manipulation. Vasoactive drugs such as phenylephrine and CO_2 can have a general systemic and/or local action. In this case, it appears that some of the RBC velocity increase with CO_2 was mediated by local vasodilation. This is consistent with the finding of local vessel diameter changes with CO_2 seen by Miles and Nuttall.[40] Thus, a particular and unique strength of the IVM technique lies not only in its ability to provide a quantitative measure of the changes in CBF, but also to provide information that permits us to identify the elements responsible for the observed change.

There are several advantages of the LD system, particularly for clinical studies and research training of investigators in this area. It is commercially available, relatively inexpensive, and easily applied. It requires little more time for setup and application than that required for surgical exposure of the cochlea. Indeed, the new investigator must be cautioned that its ease of application may be deceiving. One must be concerned with subtle preparation conditions that may lead to erroneous measurements and interpretations of results with this system, such as animal motion, fluid accumulation about the probe, and changes in ambient room light. There is also inherent drift in some of the LD instruments. If adequate care is taken, however, the device can be used to perform continuous measurements over a period of hours.[45] The instrument is applied most readily to the examination of short-term changes, preferably reversible ones, so that a return to baseline may be evaluated.[15,23,46] This consideration must be applied similarly to all other measures of CBF currently available.

The LD technique is relatively noninvasive and nondestructive. It allows a continuous, instantaneous readout of CBF. This advantage is most helpful when one is studying rapid, transient changes in flow, such as those accompanying a bolus injection of phenylephrine (Fig 4). With this drug, the CBF change begins within 1 to 2 seconds, attains rates of change on the order of 10% per second, peaks in about 10 to 15 seconds, and recovers in 2 to 5 minutes. With application of PEEP, CBF declines rapidly following blood pressure. However, independent of blood pressure, CBF tends to return to baseline over a few minutes. We interpret such recovery of CBF, in the presence of maintained blood pressure, as indicative of cochlear autoregulation.[15,16] The fact that velocity changes less than blood pressure during this manipulation, as measured by IVM, may also be explained by autoregulation (M. J. LaRouere et al, unpublished data). The characteristics of such rapid CBF fluctuations are difficult or impossible to study with other techniques.

Characterization of the dose-response relationship of various manipulations and agents is readily obtained with the LD technique. This is illustrated with electrical stimulation.[39] It also has been demonstrated with angiotensin II, nicotine, and cooling.[44,47,48]

As a final observation on the use of these techniques, it is important to realize that IVM and LD flowmetry can be combined readily for simultaneous measurement from the same cochlear turn. Appropriate optical filters in the two instruments maintain a segregation of their respective light energies. Their simultaneous use will help determine the relationship of LD flowmetry to the underlying flow as both capillary hematocrit and RBC velocity can be determined by IVM. To the extent that we know the performance of the LD flowmeter in idealized test models of circulatory systems, the comparative measures will help clarify the true sampled tissue volume of the LD technique. Laser Doppler responses that differ from IVM responses could well reflect larger sample vessels that contribute to the measured response, including deep vessels of the cochlea. Refinements in LD probe design and other technologic developments could shape this instrument for more accurate and cochleographic application.

CONCLUSIONS

In the Introduction, we note the need for objective and specific assessment of normal CBF, of its changes with disease, and its drug-dependent modulation. The data of this paper and others indicate that techniques are now available that permit studies to provide this essential information. Whole organ and regional quantitative flow measures are available with the microsphere technique. Specific and dynamic measures of RBC velocity and lumen diameter of lateral wall vessels are possible with IVM. The LD flowmeter permits linear, dynamic, and relatively noninvasive measurements of CBF that can be applied in animals and humans. We need improvements in each. Most obvious for clinical purposes is the need to calibrate the LD flowmeter. The tools are now on hand to obtain information regarding cochlear autoregulation, mechanisms of CBF control, and the influence of disease and drugs. The results of these measures indeed are complementary. In the future they will be applied systematically in conjunction with measures of metabolism, oxygen tension, and electrophysiologic measures to obtain a comprehensive understanding of the homeostatic mechanisms of the inner ear.

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COCHLEA AND HEART AS END-ORGANS IN SMALL VESSEL DISEASE

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Many studies have been done recently to determine the role of various stresses on the heart and peripheral vasculature. Although damage to coronary arteries and renal vessels has been well described, the ear as an end-organ in small vessel disease has been largely neglected. In a previous study, we examined the effects of noise, hypertension, and an atherogenic diet on the microvasculature of the cochleas in rats. The present study examines the effects of these stresses on the hearts of the same rats. The technique used to examine microvascular blood flow was the injection of unlabeled microspheres prior to killing. We found that the blood flow in the cochleas was reduced significantly in hypertensive animals exposed to noise or an atherogenic diet compared to that of normotensive or hypertensive control animals. The hearts of such animals, however, showed decreased myocardial blood flow only when compared to those of normotensive control animals, not when compared to those of hypertensive control animals.

KEY WORDS — atherosclerosis, blood flow, cochlea, hypertension, small vessel disease, tinnitus.

INTRODUCTION

The identification of various risk factors in the development of cardiovascular disease has been the subject of many population investigations.[1-5] The delineation of these risk factors and their causes has taken many years of careful analysis. Some of the identified risk factors include hypertension, smoking, hyperlipoproteinemia, obesity, diabetes mellitus, sedentary life-style, and various environmental stresses.[6-8] The primary goal of much of this research has been to decrease risk factors and thereby to attempt to prevent the development of small vessel disease in affected end-organs.

Many tissues have been identified as end-organs in small vessel disease associated with atherosclerosis. These include the retina, heart, kidneys, and lungs.[9] There have been a number of studies to examine the effects of hypertension on the vasculature of the cochlea,[10-12] but until recently there has been no technique for examining the blood flow to various parts of the cochlea separately. A technique using injection of unlabeled, carbonized microspheres into the systemic circulation has been developed that can be used to measure blood flow in virtually any tissue in the body.[13-16]

The purpose of this study is to examine the effects of three cardiovascular stresses — noise, hypertension, and hyperlipidemia — on the cochlear and coronary blood flow in an animal model.

MATERIALS AND METHODS

Two strains of rats were used in the study: normotensive Wistar-Kyoto rats (WKY) and spontaneously hypertensive rats (SHR). Thirty-two rats of each type were divided into groups as shown in Fig 1. All measurements were conducted in a double-blind fashion.

Half of the animals were exposed to noise, while the other half remained in a quiet environment (Fig 1). Animal groups exposed to noise were exposed to random length 95-dB white noise (2 to 30 kHz) for 6 months. Noise exposure and intervals varied from 1 ms to 1 second, 50% time on/off for 8 hours a day continuously for 6 months. The noise was stopped 1 month prior to killing the animals.

The groups were further divided so that one half were fed an atherogenic diet while the other half were fed a regular laboratory diet (Fig 1). The animals fed atherogenic diets were on this diet exclusively from 6 months of age to 1 year of age (see Table). This diet was designed to reproduce the high cholesterol, high triglyceride diet commonly found in an average human diet. Careful attention was paid to maintaining fat-soluble vitamin content, as rats normally eat a vegetarian diet and are subject to vitamin and other nutritional imbalances from an atherogenic diet.

Blood flow to the coronary arteries and cochleas was determined after unlabeled microsphere (10 μm) injection into the left atrium of the anesthetized animal just prior to killing. Reference blood samples were taken from an iliac artery catheter (Fig 2). Sphere dose was calculated according to each animal's body surface area (BSA) using the equation BSA = K x W, where K is a species-specific constant (9.0 for the rat) and W is the animal's weight.[17] The withdrawal rate from the iliac artery catheter was exactly the same as the injection rate into the left atrial catheter (0.217 mL/min). All animals were killed by injection of potassium chloride under gen-

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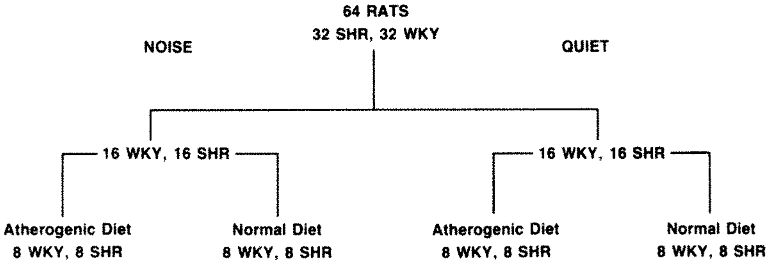

Fig 1. Division of experimental groups. SHR — spontaneously hypertensive rats, WKY — Wistar-Kyoto rats.

eral anesthesia 2 minutes after the infusion was completed. The cochleas, hearts, and kidneys were immediately removed, and the cochleas were fixed in a glutaraldehyde-formaldehyde solution. The hearts and kidneys were weighed and frozen for analysis at a later time.

Determination of the accuracy of the blood flow measurements by microsphere technique was confirmed in each animal by measuring the renal blood flow to each kidney. The values from both kidneys were compared to each other and to known renal blood flow measurements in rats.[18]

Blood flow was calculated from the formula:

$$\text{Blood flow} = \frac{\text{No. spheres in tissue}}{\text{No. spheres in reference blood}} \times (0.217 \text{ mL/min})$$

Under an operating microscope, the heart of each animal was divided according to the right and left ventricles. These specimens then were washed and weighed. Great care was taken to wash the lining of the left ventricle of any debris in order to avoid falsely elevated microsphere counts. Each ventricle then was dissolved, and microsphere counts were done on a Coulter counter.

The cochleas were prepared by the surface preparation technique using chemical decalcification of the bony capsule and dissection in layers until only a thin layer remained. The modiolus, lateral wall structures, and basilar membrane were dissected free of surrounding tissue and placed on slides. Microspheres were counted under a microscope in the central portion (modiolus), spiral portion (basilar membrane and osseous spiral lamina), and lateral portion (spiral ligament and stria vascularis) in quartered segments from hook to apex. These data were used to calculate blood flow to individual portions of the cochlea.[19]

HIGH FAT DIET FED TO HALF OF EXPERIMENTAL ANIMALS

Casein	25.0%
Sucrose	38.0%
Coconut oil (hydrogenated)	14.0%
Salt mix	4.0%
Cellulose	15.0%
Vitamin diet fortification	1.0%
Cholesterol	2.5%
Cholic acid	0.5%
Total	100.0%

All statistical analysis was done by Student's *t*-test using paired variables. Data were considered statistically significant only for $p < .05$.

RESULTS

As would be expected, blood pressure was consistently higher in the hypertensive rats than in the normotensive animals. This was true whether or not the groups were exposed to an atherogenic diet, noise, or both.

Serum cholesterol and triglyceride levels were higher in groups exposed to the atherogenic diet than in groups on normal diets ($p < .05$) (Fig 3). The only exception was for the hypertensive group in a quiet setting and on a normal diet, which showed normal triglyceride levels but slightly increased cholesterol levels.

Cochlear Blood Flow. As can be seen from Fig 4, blood flow in the spiral and lateral portions of the cochlea was significantly less in the hypertensive rats on an atherogenic diet, whether exposed to noise or not, than in all other groups ($p < .05$). These data are significant when compared to those from normotensive or hypertensive control groups. These differences were especially prominent in the stria vascularis in the first and second turns of the cochlea. All of the normotensive and hypertensive groups not exposed to atherogenic diets showed the same cochlear blood flow rate as in the control groups.[19] The common factor among all groups demonstrating significant decreases in cochlear blood flow was the atherogenic diet. Noise exposure did not cause significant differences in blood flow to any region of the cochlea examined. There was no difference between right and left ears.

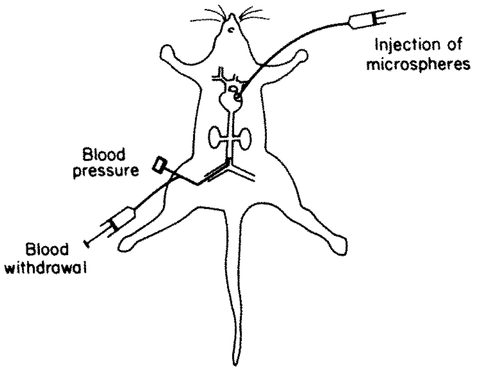

Fig 2. Determination of blood flow.

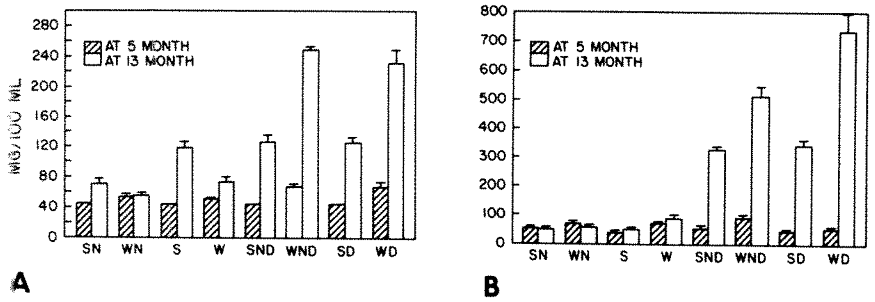

Fig 3. Determinations of A) serum cholesterol and B) serum triglycerides. SN — spontaneously hypertensive rat exposed to noise, WN — normotensive rat exposed to noise, S — spontaneously hypertensive rat, W — normotensive rat, SND — spontaneously hypertensive rat exposed to noise and fed atherogenic diet, WND — normotensive rat exposed to noise and fed atherogenic diet, SD — spontaneously hypertensive rat fed atherogenic diet, WD — normotensive rat fed atherogenic diet.

Coronary Blood Flow. Coronary blood flow was determined individually for the left ventricle, right ventricle, and the whole heart. The results of these measurements are presented in Fig 5.

When blood flow in the whole heart was examined, a significant decrease (p< .05) was found in hypertensive groups exposed to noise, atherogenic diet, or both when compared to normotensive control animals (p< .05). However, these results were not significant when compared with those from hypertensive control animals.

For the left ventricle, there was a statistically significant decrease in coronary blood flow when the hypertensive animals exposed to either noise alone or diet alone were compared to normotensive control animals. Again, these groups showed significantly decreased coronary blood flow only when compared to normotensive control animals, not when compared to hypertensive control animals.

For the right ventricle, coronary blood flow was reduced significantly in the hypertensive rats exposed to noise alone, the atherogenic diet alone, and the combination of both as compared to that of normotensive control animals. Once again, there was no significant difference from hypertensive control animals.

In summary, the significant decreases in coronary blood flow noted above were only in comparison to normotensive control animals. When these same groups were compared to hypertensive control animals, the differences were not statistically significant. This finding does not hold true for the previously reported portion of the study measuring cochlear blood flow. The decreases in cochlear blood flow were significant in the experimental animals compared to both normotensive and hypertensive control animals (p< .05).

DISCUSSION

Statistical analysis of the data clearly shows that hypertension is the key factor in the development of coronary microvascular disease. The decrease in coronary blood flow observed in the hypertensive groups exposed to noise and an atherogenic diet was significant only when they were compared to normotensive control animals. These same hypertensive groups did not demonstrate a significant reduction in coronary blood flow when compared to hypertensive control animals. In the statistical analysis of the cochlear blood flow, however, hypertensive groups exposed to noise or the atherogenic diet showed significantly decreased flow when compared to either normotensive of hypertensive control animals. None of the normotensive groups developed significant reductions in blood flow in either the heart or the cochlea.

While cochlear blood flow and coronary blood flow were found to be decreased, renal blood flow in all groups was found to be consistent with previously established normal values. This can be explained by the fact that the kidney contains an autoregulatory mechanism for the protection of microvascular beds, whereas the other two organs are not similarly shielded. For the short duration of this study, renal autoregulatory mechanisms remained functional. Many investigators have shown decreased renal blood flow in aged hypertensive rats. We have corroborated these findings.[19]

There have been many studies to examine the effects of stresses such as an atherogenic diet on the

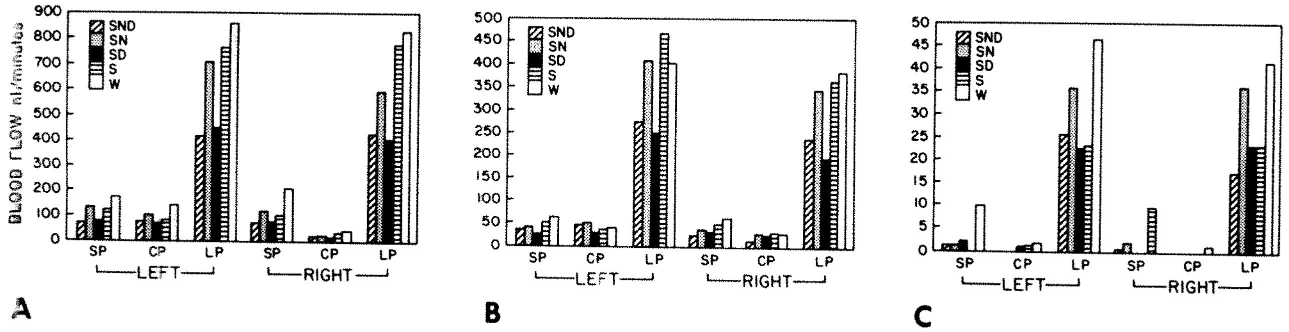

Fig 4. Cochlear blood flow in A) turn 1, B) turn 2, and C) turn 3. SP — spiral portion, including basilar membrane, CP — central portion, including modiolus, LP — lateral portion, including stria vascularis. See Fig 3 for key to other abbreviations.

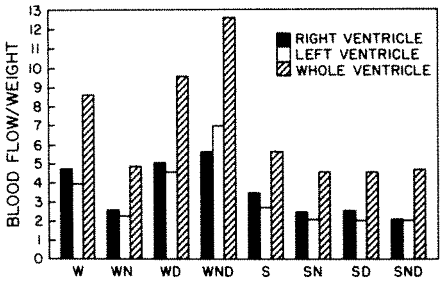

Fig 5. Coronary blood flow. See Fig 3 for key to abbreviations.

microvasculature of various organs, especially on the cardiovascular system. Certain of these stresses can be seen earliest in organs other than the heart, such as in microvascular disease of the eye or in the early forms of hypertensive kidney disease.[9] In this study we have chosen to examine the effects on small vessel blood flow in two end-organs (the heart and cochlea) under three types of stresses separately and in combination. It has been suggested that tinnitus or certain types of presbycusis may precede cardiac or peripheral vascular manifestations of stress-induced small vessel disease.[20] This study is the first to demonstrate in a controlled laboratory setting that microvascular disease of the inner ear may precede other manifestations of cardiovascular disease.

The requirements that must be fulfilled for the use of this technique of blood flow measurement have been defined previously.[21] These are as follows:

1. The microspheres must not recirculate. It has been shown that 10-μm microspheres will be trapped on the first pass by capillaries in the cochlea, heart, kidney, and other organs.[16,22,23]
2. There must be uniform mixing of microspheres and blood of the left ventricle and even distribution of the microspheres in the body's capillaries. We have demonstrated this by confirming equivalent blood flow in both kidneys of each animal and also by favorable comparisons of these values with known values of rat renal blood flow.[19]
3. The blood flow should not be affected adversely by the microspheres. Spheres under 17 μm repeatedly have been shown not to change the distribution of cardiac blood flow.
4. To avoid random error there must be at least 400 microspheres in each tissue sample being examined as well as in the reference blood sample. Although some of the cochlear sections barely showed 400 microspheres, we felt that this was not a significant problem because intra-aural differences in blood flow for specific areas of the cochlea within each rat were negligible. All other tissues examined showed well over 400 microspheres per sample.
5. The microspheres should not be degraded within the tissues into which they are deposited.[18,22] This requirement was fulfilled in that all animals were killed immediately following microsphere injection.

CONCLUSIONS

This study demonstrates that although hypertension, prolonged noise, or an atherogenic diet has clear effects on the microvascular blood flow within the heart, their effects on the microvascular circulation within the cochlea are even greater. It is possible that patients in whom these signs are present may benefit from early intervention or removal of the stresses causing these changes in the microcirculation. When older patients develop unexplained tinnitus or sensorineural hearing loss, then serum lipoprotein levels and other measures of atherosclerosis should be evaluated carefully.

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EIGHTH SHAMBAUGH/SHEA INTERNATIONAL WORKSHOP ON OTOLOGY

The Eighth Shambaugh/Shea International Workshop on Otology will be held March 3-6, 1988, at the Marriott Hotel in downtown Chicago. For further information, contact Ruth C. Enquist, We Plan Meetings, Inc, 1503 - 15th Street NE, Rochester, MN 55904; (507) 285-1523.

GERMAN SOCIETY OF OTO-RHINO-LARYNGOLOGY, HEAD AND NECK SURGERY

The 59th Annual Congress of the German Society of Oto-Rhino-Laryngology, Head and Neck Surgery will be held May 15-19, 1988, in Nuremberg, Federal Republic of Germany. For further information, contact Prof Dr K. Fleischer, Hittorfstr 17, D-5300 Bonn 1, Federal Republic of Germany.

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MULTIPLE OTOPATHOLOGIC DISORDERS

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Temporal bones (1,383) from 713 patients were studied systematically for multiple pathologic lesions. Eleven percent (152 temporal bones) were found to have more than one pathologic finding. Males (60.5%) had multiple diseases more commonly than did females (37.7%). The most frequently occurring findings were otitis media (71.1%), otosclerosis (43.4%), endolymphatic hydrops (38.8%), labyrinthitis (25.0%), and cancer (24.3%). We conclude that multiple coexisting pathologic conditions can have coincidental or causative relationships. The otolaryngologist should consider multiple pathologic conditions when diagnosing and treating diseases of the ear.

KEY WORDS — cancer, endolymphatic hydrops, labyrinthitis, otitis media, otosclerosis, temporal bone.

INTRODUCTION

It is axiomatic of medicine in general and of otology in particular that diagnosis of disease depends upon an understanding of the causative factors that initiate the disease and of the pathogenesis — the mechanisms or processes that transpire between the cause and the end state of the pathologic or pathophysiologic condition, usually manifested by symptoms, that brings the patient to the otolaryngologist's office. The history and physical examination, including otoscopy, are most important in otologic diagnosis. For some otologic diseases, studies such as radiography or computed tomography can aid the diagnostic process. Audiology helps determine the magnitude and nature of the hearing loss and can assist in determining the site of lesion, eg, middle ear, labyrinth, or retrocochlear area. However, pathologic findings in general for medicine and in the temporal bone in particular for otology remain perhaps the most significant correlate for diagnosis and therefore for treatment of disease.[1]

In otologic diagnosis, general or systemic diseases as well as local disease should be considered and judgments or inferences made of interrelationships concerning causation or coincidence. For example, a patient with sensorineural hearing loss or vestibular symptoms may have cardiovascular disease or diabetes mellitus that is coincidental, whereas another patient with similar symptoms may have syphilis with causative implications.

Otologic diseases can occur as complications or sequelae from other otologic diseases. For example, tympanogenic labyrinthitis (hearing loss and vertigo) or paralysis of the facial nerve can occur as complications of cholesteatoma, tumors in the middle ear, or otitis media. Conductive hearing losses (tympanosclerosis, ossicular fixation or disruption, atelectasis) or sensorineural hearing losses can occur as sequelae of otitis media.[2-4] Otologic diseases, eg, meningogenic labyrinthitis, also can occur as a complication of a regional disease, eg, meningitis, or sometimes vice versa.[2] Although the importance of pathologic findings in diagnosis and treatment of disease is a generally accepted principle, occasionally at autopsy and in otopathologic assessment pathologic lesions are seen that are silent and have not led to symptoms or complaints. Silent otitis media, that is, intractable pathologic conditions behind an intact tympanic membrane, can be an example of this phenomenon.[5]

Just as systemic illnesses often coexist with otologic disease, either in a causative or coincidental way, we have observed on many occasions clinically (during otologic surgery) or in the otopathologic laboratory that more than one pathologic lesion can coexist in the same temporal bone. For this reason, we undertook this study to assess evident multiple pathologic conditions in the same temporal bone. It is hoped that this information will assist the otologist in diagnosing diseases of the ear.

MATERIALS AND METHODS

Thirteen hundred eighty-three temporal bones from 713 patients were examined for the presence of multiple pathologic conditions. A temporal bone was classified as having multiple pathologic conditions if it contained more than one of the following findings: otosclerosis, acoustic neuroma, cancer, arteritis in the middle ear, bulging round window membrane, fungus in the inner ear, hemorrhage in the inner ear, Mondini dysplasia, endolymphatic hydrops, otitis media, labyrinthitis. The category of otitis media was divided into the following classification — serous otitis media, purulent otitis media, mucoid otitis media, and chronic otitis media — or listed as a combination of these types of otitis media.

From the Otopathology Laboratory, Department of Otolaryngology, University of Minnesota, Minneapolis. Supported in part by National Institutes of Health grant NS 14538, the International Hearing Foundation, and the Deafness Research Foundation.

Presented at the meeting of the American Otological Society, Inc, Denver, April 26-27, 1987.

REPRINTS — M. M. Paparella, MD, 701 25th Ave S, Minneapolis, MN 55454.

TABLE 1. FREQUENCY OF PATHOLOGIC CONDITIONS IN EARS WITH MULTIPLE PATHOLOGIC CONDITIONS

Conditions	*No. Ears*	*% Ears*
Otitis media	108	71.1
Otosclerosis	66	43.4
Endolymphatic hydrops	59	38.8
Labyrinthitis	38	25.0
Cancer metastatic to ear	37	24.3
Acoustic neuroma	7	4.6
Hemorrhage in inner ear	5	3.3
Mondini dysplasia	4	2.6
Arteritis in middle ear	4	2.6
Fungus in inner ear	3	2.0
Bulging round window membrane	2	1.3
Fracture of temporal bone	1	0.7

The classification of otitis media was based on the characteristics of middle ear effusions and pathologic changes of chronic inflammatory reaction as follows: serous otitis media, a serous effusion in the middle ear cavity containing only a few inflammatory cells and no epithelial hyperplasia; seropurulent otitis media, a serous effusion containing moderate numbers of inflammatory cells with no epithelial hyperplasia; purulent otitis media, a large number of inflammatory cells with epithelial hyperplasia; mucoid otitis media, mucoid effusion in addition to hyperplastic and hypersecretory changes of the mucoperiosteum; chronic otitis media, intractable pathologic tissue such as cholesteatoma, cholesterol granuloma, or granulation tissue.

Labyrinthitis was divided into purulent, fibrous, and osseous types as follows: purulent labyrinthitis, inflammatory cells within the inner ear; fibrous labyrinthitis, proliferation of fibrous tissue; osseous labyrinthitis, bone within the inner ear.

Temporal bones were not examined for subtle changes such as minute fractures, losses of hair cells or ganglion cells, or pathologic changes of the organ of Corti or stria vascularis. Clinical histories were not used to categorize a temporal bone as having multiple disorders. Classification of temporal bones with multiple disorders was based only on the histopathologic findings. Biographic data and histopathologic findings in temporal bones were tabulated, and the data were examined for comparison and correlation.

RESULTS

Of the 1,383 temporal bones (713 patients) examined, 152 temporal bones (114 patients) or 11% were found to have multiple pathologic conditions. The patients included 69 males, 43 females, and two patients of unknown sex; the known percentages were 60.5% male and 37.7% female. One hundred forty-five of the patients were white (95.4%), one was black (0.7%), three were American Indians (2.0%), and for three the information was not available.

TABLE 2. FREQUENCY OF BILATERAL PATHOLOGIC CONDITIONS (98 TEMPORAL BONES, 49 PATIENTS)

Conditions	*No. Pts*	*% Pts*
Otitis media	28	75.7
Otosclerosis	19	51.4
Labyrinthitis	11	29.7
Endolymphatic hydrops	9	24.3
Cancer metastatic to ear	6	16.2

The frequencies of pathologic conditions occurring in all ears with multiple pathologic conditions are listed in Table 1. The most frequently occurring findings were otitis media (which occurred in 108 ears or 71.1%), otosclerosis (66 ears, or 43.4%), endolymphatic hydrops (in 59 ears, or 38.8%), labyrinthitis (which occurred in 38 ears, or 25.0%), and cancer metastatic to the ear (in 37 ears, or 24.3%). The remaining pathologic conditions each occurred in fewer than 5% of the ears. The condition with the lowest frequency, fracture of the temporal bone, occurred in 0.7% of the ears.

The 108 temporal bones having otitis media as well as at least one other coexisting pathologic finding constituted approximately 22.9% of the total number of bones with otitis media in our collection. The 66 temporal bones having otosclerosis and at least one other pathologic finding represented about 49% of our otosclerotic temporal bones. Of the total number of temporal bones in our collection that had acoustic neuromas, 58% had at least one other coexistent pathologic finding.

Within the category of otitis media plus another condition (108 ears), chronic otitis media occurred in 62 ears (57.4%), purulent otitis media in 20 ears (18.5%), serous otitis media in seven ears (6.5%), chronic mucoid otitis media in two ears (1.9%), mucopurulent otitis media in one ear (0.9%), seropurulent otitis media in 14 ears (12.9%), and chronic mucopurulent otitis media in two ears (1.9%). The category of labyrinthitis consisted of the following types: purulent, 20 ears (52.6%); fibrous, six ears (15.8%); and osseous, 12 ears (31.6%).

The most common categories of otitis media, labyrinthitis, otosclerosis, endolymphatic hydrops, cancer metastatic to the ear, and acoustic neuroma were selected for further evaluation. The other categories were not further evaluated because of their infrequent occurrence.

Bilateral multiple pathologic conditions were observed in 74 ears (37 patients). The frequencies of pathologic conditions occurring in both ears are listed in Table 2. Otitis media was found bilaterally in 75.7% of the patients, labyrinthitis in 29.7%, otosclerosis in 51.4%, endolymphatic hydrops in 24.3%, and cancer metastatic to the ear in 16.2%.

Two pathologic conditions occurring in the same ear were observed in 110 ears, three pathologic con-

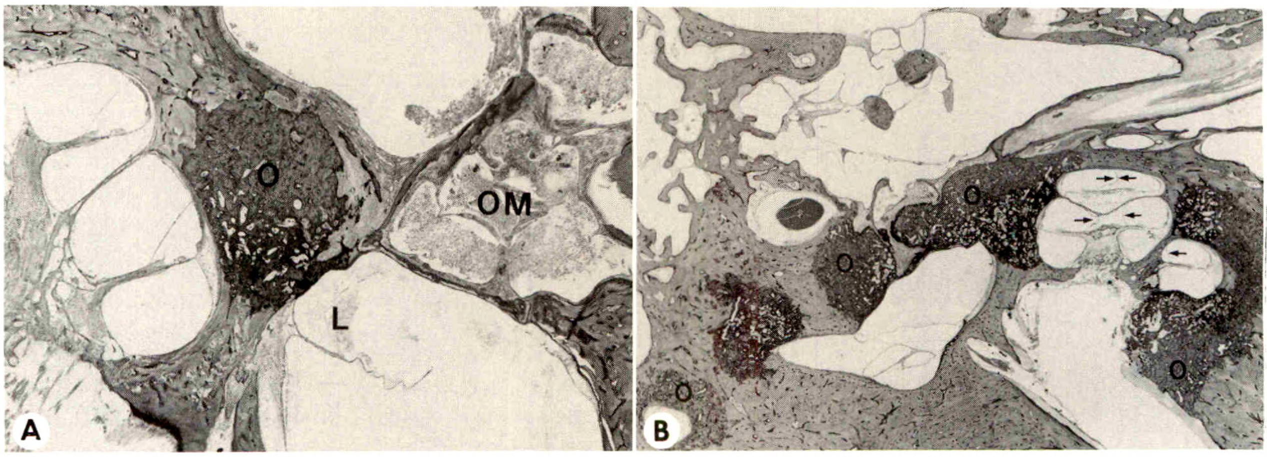

Fig 1. Photomicrographs of temporal bone damage in patients with multiple pathologic findings. A) Sixty-two-year-old man had bilateral mixed hearing loss; onset was at 15 years of age (original x15). Preexisting otosclerosis (O) was probably followed by coincidental otitis media (OM) and labyrinthitis (L). B) Patient had clinical history of Meniere's disease (original x8). Extensive otosclerosis (O) probably preceded Meniere's disease and endolymphatic hydrops (arrows), demonstrating possibly causative relationship.

ditions in the same ear in 37 ears, and four in the same ear in five ears. No more than four pathologic conditions were observed in any ear. Of the 108 temporal bones with multiple pathologic findings that included otitis media, labyrinthitis was found as a coexistent condition in 24 ears, otosclerosis in 35 ears, endolymphatic hydrops in 29 ears, metastatic cancer in 24 ears, and acoustic neuroma in two ears. Coexistent pathologic conditions in the 66 ears with otosclerosis were otitis media (35 ears), endolymphatic hydrops (29 ears), labyrinthitis (13 ears), metastatic cancer (eight ears), and acoustic neuroma (two ears). The coexistent pathologic findings in the 39 ears with labyrinthitis were otitis media (24 ears), otosclerosis (13 ears), metastatic cancer (six ears), and acoustic neuroma (two ears). Those 59 ears with endolymphatic hydrops had otitis media in 29 ears, otosclerosis as the coexistent pathologic finding in 29 ears, metastatic cancer in 8 ears, and acoustic neuroma in two ears. Cancer metastatic to the ear occurred in 37 ears with coexistent pathologic findings including otitis media (24 ears), labyrinthitis (six ears), endolymphatic hydrops (eight ears), and otosclerosis (eight ears). The seven ears with acoustic neuroma had the following additional findings: labyrinthitis (two ears), hydrops (two ears), otosclerosis (two ears), and otitis media (two ears).

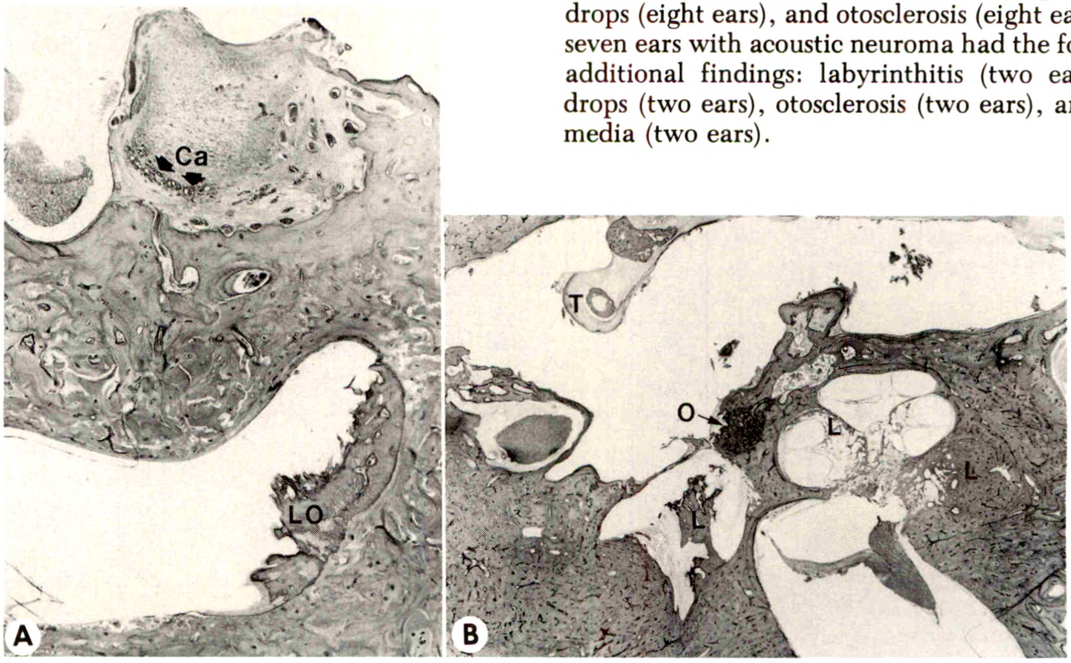

Fig 2. Photomicrographs of temporal bone damage in patients with multiple pathologic findings. A) Seventy-five-year-old man had right Bell's palsy, decompressed after facial nerve was affected by metastatic cancer (Ca) from prostate (original x20). He also had labyrinthitis ossificans of the lateral semicircular canal (LO), a coincidental finding. B) Seventy-three-year-old woman had history of chronically draining ears, tympanosclerosis (T), otosclerosis (O), labyrinthitis ossificans (L) with endolymphatic hydrops, and bilateral profound deafness since scarlet fever at age 25 (original x8). Cause-and-effect relationship of labyrinthitis after otitis media is possible; cause-and-effect relationship of otitis media and labyrinthitis to otosclerosis is unlikely.

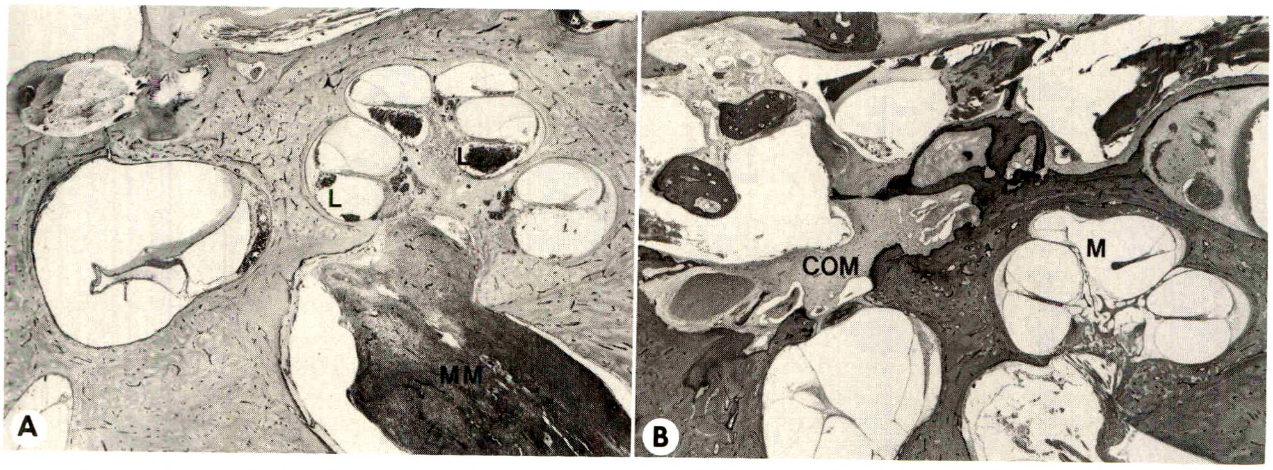

Fig 3. Photomicrographs of temporal bone damage in patients with multiple pathologic findings. A) Fifty-one-year-old man had malignant melanoma (MM) with metastasis to seventh and eighth cranial nerves and purulent, hemorrhagic labyrinthitis (L) with endolymphatic hydrops (original x10). He had bilateral hearing loss and history of dizziness for 2 months. Cause-and-effect relationship of melanoma to labyrinthitis likely. B) Fifty-year-old woman had acute myelogenous leukemia, chronic otitis media (COM) plus Mondini dysplasia (M), left otalgia, otorrhea, and progressive deafness (original x9). Pathologic findings probably coincidental.

Examples of multiple pathologic findings, with estimates of causation or coincidence, are seen in Figs 1 through 4.

DISCUSSION

Since the contributions of the European otopathologists at the turn of the century, otopathology has been and remains an important clinical and research objective in diagnosis and treatment of otologic disease. Although many authors have discussed specific otopathologic findings or correlates for certain diseases, we could find no systematic study of multiple pathologic conditions within a given temporal bone. Pathologic findings assessed in this study were based on our previous experience and assessment of this material, and for this reason were determined somewhat arbitrarily. Not all pathologic findings were documented, and certainly not the many detailed findings, eg, cellular details of the membranous labyrinth. In this study, pathologic findings were assessed exclusive of the clinical records including audiologic data. Since pathologic conditions occasionally can be silent, although usually accompanied by symptoms, in a subsequent study we intend to correlate the clinical records, including the audiologic data, with the multiple pathologic findings.

Using the criteria in this study, 11.0% (152) of the total number (1,383) of temporal bones assessed had more than one pathologic finding. Bilateral multiple pathologic conditions were seen in 74 of these 152 temporal bones. The percentage of males (60.5%) was significantly higher than that of females (37.7%), perhaps because males have more

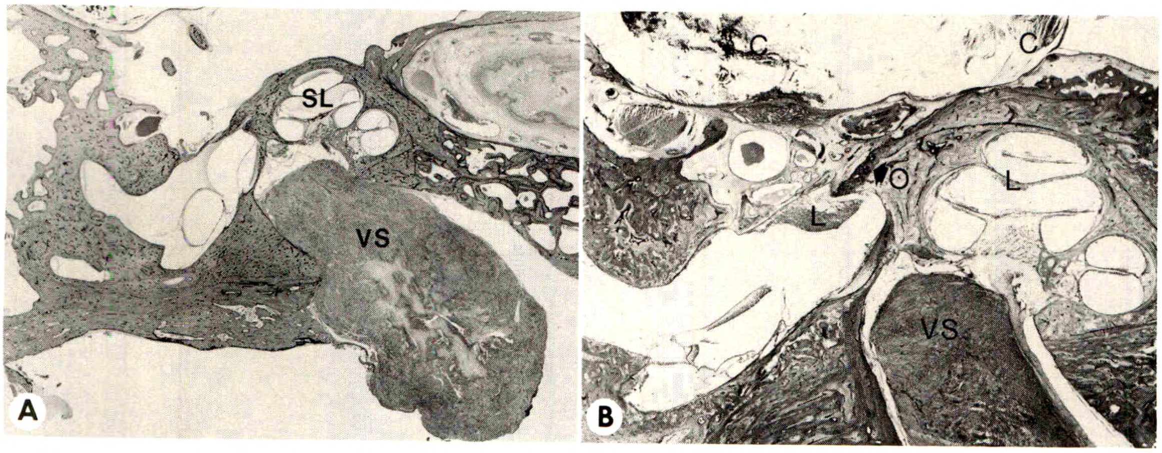

Fig 4. Photomicrographs of temporal bone damage in patients with multiple pathologic findings. A) Seventy-six-year-old man had left severe sensorineural hearing loss and history of dizziness (original x5). He had vestibular schwannoma (VS) and serous labyrinthitis (SL) with slight endolymphatic hydrops. Possible cause-and-effect relationship may exist between schwannoma and serous labyrinthitis. B) Eighty-six-year-old woman was congenitally deaf with familial history of hearing loss (original x15). She had chronic otitis media with cholesteatoma (C), otosclerosis (O), vestibular schwannoma (VS), and labyrinthitis (L). Cholesteatoma with chronic otitis media, otosclerosis, and vestibular schwannoma are most likely coincidental findings; labyrinthitis could relate to chronic otitis media or vestibular schwannoma.

pathologic findings, or in lesser likelihood because of unseen biases in selection criteria.

Certain pathologic findings occurred simultaneously more frequently than did others, some in unexpected combinations. Of the 108 temporal bones with otitis media, 22.2% had labyrinthitis and 22.2% had ear cancer. There may be a cause-and-effect relationship. On the other hand, it was somewhat surprising to find otitis media occurring so frequently in temporal bones with otosclerosis. Of 66 ears with otosclerosis, 53% also had otitis media. Other conditions that occurred in the temporal bones with otosclerosis were labyrinthitis (in 19.7%), endolymphatic hydrops (in 43.9%), and ear cancer (in 12.1%). With the possible exception of endolymphatic hydrops, a cause-and-effect relationship for these findings generally is not anticipated. Does this mean that one of these pathologic findings, which may be characteristic of a disease of polygenic origin, renders the temporal bone more susceptible to another disease?

The recent literature suggests that certain combinations of otologic diseases such as Meniere's disease and otitis media[6] or Meniere's disease and otosclerosis[7] can occur, with possible causative relationships. Other recently described findings such as perilymphatic fistulae with Meniere's disease[8] would appear to be coincidental, although causative factors could be considered in the future.

Pathologic findings that are the end result of cause and pathogenesis are important correlates in otologic diagnosis. As described and discussed in this paper, multiple pathologic conditions can coexist in the same temporal bone, with implications of a coincidental or causative relationship. Otolaryngologists should consider this possibility when diagnosing and treating diseases of the ear.

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AMERICAN AUDITORY SOCIETY

The 15th annual meeting of the American Auditory Society will be held in Boston on Thursday, November 17, 1988. The meeting is scheduled in conjunction with the annual meeting of the American Speech-Language-Hearing Association. For further information, contact Frank E. Musiek, PhD, Program Chairman, Dartmouth-Hitchcock Medical Center, 2 Maynard Street, Hanover, NH 03756.

Ann Otol Rhinol Laryngol 97:1988

DIAGNOSIS OF RETROCOCHLEAR AND CENTRAL VESTIBULAR DISEASE BY MAGNETIC RESONANCE IMAGING

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Magnetic resonance imaging has become the study of choice for the diagnosis of retrocochlear and central vestibular disease. Three groups of lesions, each characterized by a specific site of origin, have been recognized: 1) petrous apex lesions such as congenital cholesteatomas and cholesterol granulomas involving the eighth cranial nerve within the internal auditory canal; 2) cerebellopontine angle tumors, mainly acoustic neuromas and meningiomas; and 3) CNS disease involving the brain stem and the central auditory and vestibular pathways such as tumors, multiple sclerosis, infarcts, and hemorrhage.

KEY WORDS — central vestibular disease, magnetic resonance imaging, retrocochlear disease.

Magnetic resonance imaging has become the imaging study of choice for the diagnosis of retrocochlear and central vestibular disease. Retrolabyrinthine hearing loss accounts for 20% to 22% of all cases of pure sensorineural hearing loss. Approximately 10% of the lesions are located in the cerebellopontine angle and 12% elsewhere. Vestibular disorders are of central origin in 70% of the cases.[1,2] The far more frequent occurrence of vestibular rather than auditory findings in CNS disease rests on the difference of their central pathways. Whereas the central auditory pathways are well defined from the cochlear nuclei to the auditory cortex, the vestibular pathways are more complex because of extensive distribution and connection of their fibers in the brain stem and cerebellum. It is the purpose of this paper to review the MRI findings in the most common pathologic processes producing retrocochlear hearing losses and retrolabyrinthine vestibular disorders. Pathologic processes may occur at three sites: 1) in the petrous pyramid with involvement of the eighth cranial nerve within the internal auditory canal; 2) in the cerebellopontine angle; and 3) in the brain, mainly in the brain stem and cerebellum.

METHOD

All scans were performed with a GE Signa unit at 1.5 tesla. The protocol varied for the three sites of disease as follows.

For disease of the petrous pyramid, axial 3-mm contiguous sections were spin density weighted at 2000TR, 20TE and T2 weighted at 2000TR, 80TE using a 16-cm field of view. Sagittal and coronal sections were spin density weighted at 1500TR, 25TE using a 7.5-cm (3 in) surface coil.

For disease of the cerebellopontine angle, coronal 3-mm contiguous sections were T1 weighted at 600TR, 25TE using a 16-cm field of view. Axial 3-mm contiguous sections were spin density weighted at 2000TR, 20TE and T2 weighted at 2000TR, 80TE using a 24-cm field of view.

For disease of the brain stem and brain, 5-mm axial and coronal sections with 5-mm interspace gaps were spin density weighted at 2000TR, 20TE and T2 weighted at 2000TR, 80TE using a 24-cm field of view.

The images were acquired using two or four excitations and a 256 x 128 matrix.

SELECTION OF PATIENTS

Auditory and vestibular tests were used to differentiate patients with peripheral or labyrinthine lesions from patients with retrolabyrinthine or CNS disease. Auditory assessment included a pure tone audiogram, speech discrimination tests, impedance studies, and auditory brain stem evoked response. The vestibular assessment was performed at our institution with photoelectric nystagmography for recording of eye movement and the Torok monothermal differential caloric test. Spontaneous nystagmus, vestibular decruitment, and nonfatiguing reproducible posturally induced nystagmus were the most common findings indicative of central disease.

RESULTS

Petrous Pyramid Lesions. These lesions produce a retrolabyrinthine hearing loss and vestibular findings whenever they erode the internal auditory canal and involve the cochlear and vestibular nerves. Congenital cholesteatomas and cholesterol granuloma cysts produce similar findings and are often indistinguishable by computed tomography. Both processes are characterized by an expansile le-

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Presented at the meeting of the American Otological Society, Inc, Denver, April 26-27, 1987.

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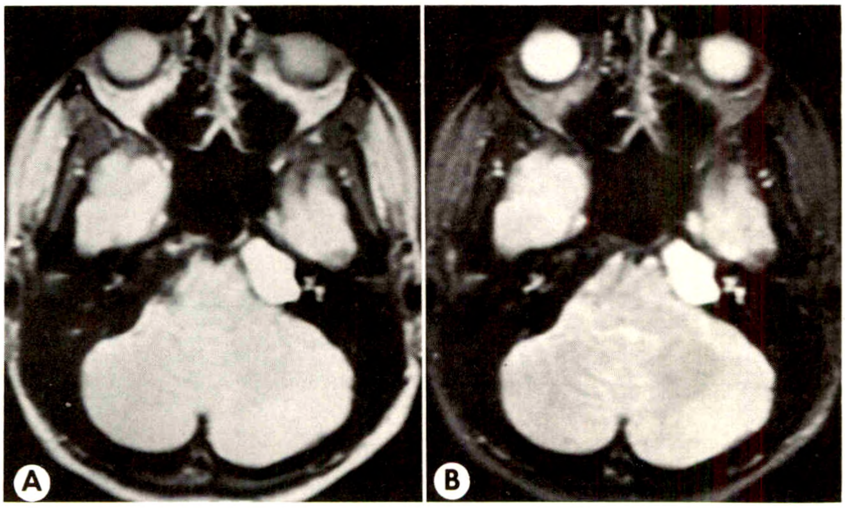

Fig 1. Cholesterol granuloma of left petrous apex. A,B) Axial sections show large lesion characterized by high and homogeneous intensity signal. A) T1 weighted sequence, B) T2 weighted sequence.

sion in the petrous apex filled by a low attenuation mass. Postinfusion CT sections reveal a faint and often incomplete ringlike enhancement of the capsule. The two lesions can be differentiated by MRI. Congenital cholesteatomas appear as areas of medium signal intensity in the T1 and spin density weighted images but of high intensity in the T2 weighted images. Cholesterol granulomas instead give a high intensity signal in both T1 and T2 weighted images because of short T1 and long T2 relaxation times (Fig 1). In both sequences the mass may be nonhomogeneous in intensity because of the presence of a low signal, presumably hemosiderin. Glomus tumors may occasionally involve the petrous pyramid and internal auditory canal while sparing the other inner ear structures and the middle ear cavity. The tumor appears on MRI as a mass of medium signal intensity often containing a fine dark pattern produced by blood vessels. Both intracranial and extracranial involvement can be defined more precisely than with CT. In addition, involvement of the jugular vein and carotid artery are readily demonstrated, thus avoiding the need for invasive vascular studies.

Cerebellopontine Angle Lesions. Acoustic neuromas account for 90% of the cerebellopontine angle tumors. Large acoustic neuromas with an extracanalicular component of 1.5 cm or more are seen well in all sequences. The tumor is isointense or brighter than the brain, the brain stem and cerebellum are compressed, and the fifth cranial nerve is often involved.[3,4] A dark line produced by the meninges usually separates the tumor from the adjacent brain stem and cerebellum. In the T2 weighted images, the mass may be nonhomogeneous in intensity. Acoustic neuromas with an extracanalicular component of less than 1.5 cm are best seen in the T1 and spin density weighted images, where the mass appears brighter than the surrounding CSF (Fig 2A,B). In the T2 weighted images, the tumor is often not recognizable, since its signal intensity is

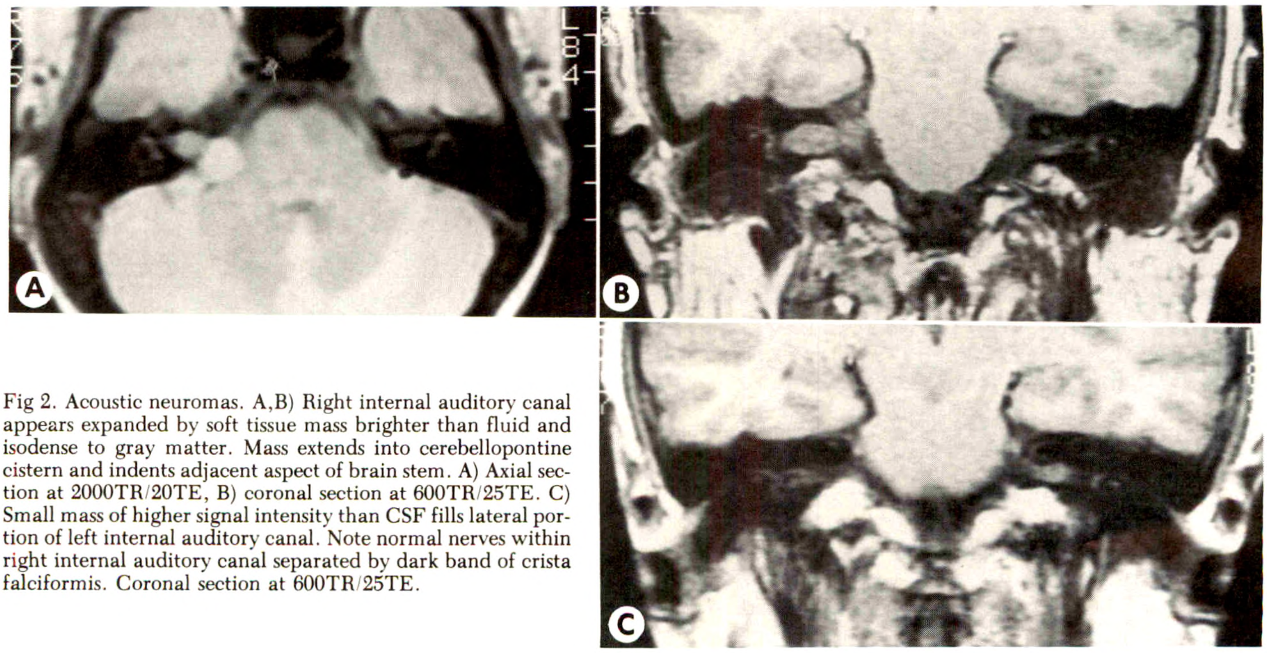

Fig 2. Acoustic neuromas. A,B) Right internal auditory canal appears expanded by soft tissue mass brighter than fluid and isodense to gray matter. Mass extends into cerebellopontine cistern and indents adjacent aspect of brain stem. A) Axial section at 2000TR/20TE, B) coronal section at 600TR/25TE. C) Small mass of higher signal intensity than CSF fills lateral portion of left internal auditory canal. Note normal nerves within right internal auditory canal separated by dark band of crista falciformis. Coronal section at 600TR/25TE.

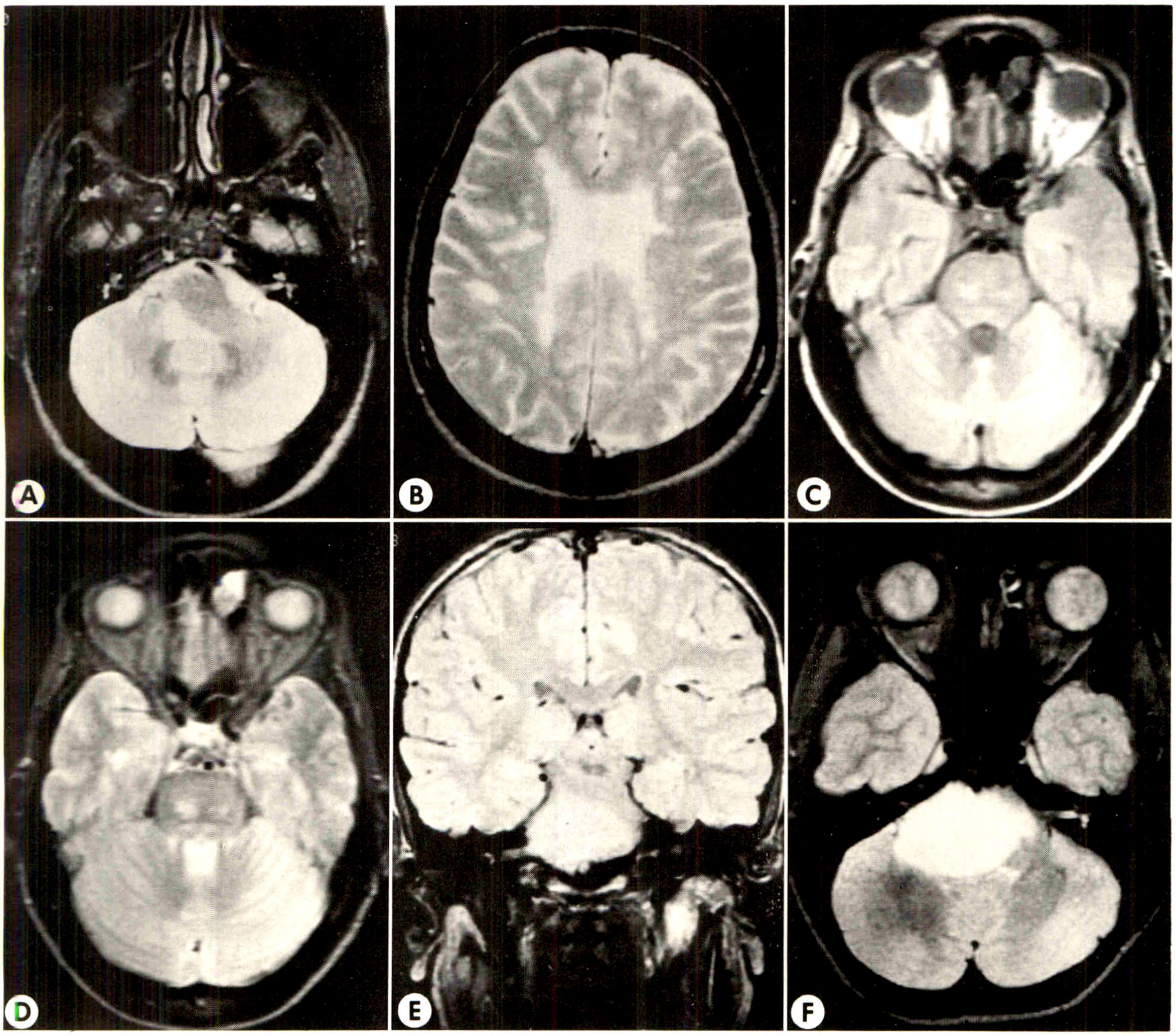

Fig 3. MRI of common pathologic conditions affecting central vestibular and auditory pathways. A,B) Multiple sclerosis on T2 weighted axial sections of posterior cranial fossa. Large area of increased signal intensity in posterior aspect of pons on right (A) and through upper portion of lateral ventricles (B). Multiple lesions in periventricular white matter are seen in B. Note that several plaques are oval in shape with long axis perpendicular to sagittal plane of brain. C,D) Ischemic changes on T1 weighted (C) and T2 weighted (D) axial sections. Two areas of high signal intensity are noticed in midportion of pons. Lesions are better seen in D. E,F) Brain stem glioma on T1 weighted coronal (E) and T2 weighted axial (F) sections. Large lesion involves and expands pons; it is isointense to gray matter in T1 weighted image (E) but of high signal intensity in T2 weighted section (F).

isointense to CSF. Small acoustic neuromas limited to the internal auditory canal are best seen in the T1 weighted images as areas of higher signal intensity than the normal nerve and CSF (Fig 2C).[5,6] Small lesions produce thickening of the nerve; larger masses fill a portion of or the entire internal auditory canal.

Central Vestibular Disease. Magnetic resonance imaging is far superior to CT in demonstrating disease of the posterior cranial fossa, because of the higher sensitivity of this modality to pathologic changes in the brain parenchyma and of the lack of bony artifacts that deteriorate the quality of the CT images.[7] The most common pathologic conditions affecting the central vestibular and auditory pathways are demyelinating processes, vascular abnormalities, and tumors. Plaques of multiple sclerosis, the most common of the demyelinating processes, appear on MRI as areas of increased signal intensity, particularly in the T2 weighted images. The lesions, variable in size and often confluent, are most common in the periventricular white matter and centrum semiovale. The pons, medulla oblongata, and cerebellum are often affected, hence the frequent involvement of the central vestibular and auditory pathways (Fig 3A).[8] Changes similar to those produced by multiple sclerosis are produced by microvascular disease with consequent small areas of brain tissue ischemia (Fig 3C,D). Age of the patient and location and shape of the lesions help in differentiating the two processes. Changes produced by multiple sclerosis are usually oval in shape, are periventricular or centrally located (Fig 3B), and occur before the fifth decade, whereas microvascular insults occur in older patients and are more rounded in shape and often subcortical in location. Infarcts from occlusion of large vessels, aneurysms, intracerebral bleeding, and vascular malformations are also often responsible for vestibular findings and retrocochlear deafness. Intraparenchymal hematomas older than 48 hours appear on MRI as areas of high signal intensity in both T1 and T2 weighted images because of conversion of hemoglobin into methemoglobin. Vascular malformations have a nonspecific appearance, namely a high signal intensity lesion surrounded by a ring of no signal and often containing punctate areas of low signal.[9] Finally, benign and malignant brain tumors often involve and encroach upon the auditory and vestibular pathways (Fig 3E,F). Benign lesions are well defined, usually not surrounded by edema, and often cystic in type. The signal intensity of the lesions in the various sequences depends upon the chemical characteristics of the fluid. Malignant tumors are poorly defined, usually of low or medium intensity in the T1 weighted images and high in intensity in the T2 weighted images. The lesions are surrounded by edema, which in the T2 weighted sequences is often isointense to the tumor mass, thus obscuring the margin of the lesion.

Differentiation between tumors of various histologic types is difficult at present, but it will become possible in the near future with the refinement of chemical shift imaging and spectroscopy.

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CHOLESTEATOMA IN THE PEDIATRIC AGE GROUP

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The diagnosis and management of cholesteatoma in children remains controversial. In the past 15 years, the senior author (S.C.P.) has treated 320 patients with cholesteatoma. Patients 18 years and younger composed 40% (125) of the overall group and are the basis for this report. The patient data were compiled using the history, physical examination, audiograms, radiographs, patient questionnaires, surgical findings, and postoperative observations. The surgical treatment selected was determined by the extent of disease, the configuration of the mastoid, and a clinical assessment of eustachian tube function. A middle ear tympanotomy approach was used in 17% of the patients, a canal wall up procedure in 31%, and a canal wall down procedure in 52.3%. The average clinical follow-up was 3.9 years, with the range being from 3 months to 13.5 years. Hearing was maintained or slightly improved in a majority of cases. Residual disease occurred in 8% of patients, and recurrent disease in only 3%.

KEY WORDS — pediatric cholesteatoma.

INTRODUCTION

Pediatric cholesteatoma presents the otologist with a multitude of challenges in diagnosis and treatment. Previous studies[1] have reported conflicting results, making it difficult to draw consistent conclusions regarding the clinical nature of this disease. Palva et al,[2] Glasscock et al,[3] and Jahnke[4] suggest that cholesteatoma is more aggressive in children than in adults, while Tos[5] and Sheehy[6] find pediatric cholesteatoma to be a less expansive disease with fewer complications. With respect to surgical treatment, Jansen,[7] Sheehy,[6] and Glasscock et al[3] favor a canal wall up procedure, Jahnke[4] and Palva et al[2] use a canal wall down approach more often, and Smyth[8] and Tos[5] employ both procedures. Finally, while most authors agree that recurrence and residual rates are higher in children than in adults, the incidence of these problems in children ranges widely, from 8%[8] to 51%.[6]

This paper presents the results of an extensive review of 125 patients 18 years and younger who had cholesteatomas treated surgically. The selection of the operative technique was based primarily on the extent of the disease, the clinical assessment of eustachian tube function, and the condition of the middle ear and mastoid. Other issues addressed in this study include the destructive nature of cholesteatoma, the incidence of residual or recurrent disease, the need for long-term follow-up, and the possibility of maintaining good hearing in children with cholesteatoma.

The authors have retrospectively reviewed and analyzed the diagnosis and treatment of patients with cholesteatoma operated upon by the senior author (S.C.P.) during the last 15 years at Manhattan Eye, Ear and Throat Hospital (1983 to 1986) and Mount Sinai Medical Center (1971 to 1983). In order to assure an unbiased evaluation, all data collection was performed independent of the senior author.

Hospital records, office charts, and audiometric studies served as the principal sources of clinical data. An extensive protocol was devised for collating patient information using computer technology. In addition, subjective information gathered through a patient questionnaire was used to help confirm clinical observations. Cases in which the operative reports were either incomplete or missing were excluded from the study.

CLINICAL DATA

This study was composed of 125 patients (127 ears) who were 18 years of age and younger and who were followed for a minimum of 3 months. Eighteen was selected as the cutoff age in accordance with the guidelines defining a pediatric case as established by the Department of Pediatrics at Mount Sinai Medical Center. The average age of the patients at surgery was 9.65 years, with a fairly even distribution between the ages of 2 and 18. Seventy-seven percent of the children were over 6 years of age. Of the 127 ears affected, 57 were in patients with involvement of the left ear only, 63 were in patients with involvement of the right ear only, and five patients had bilateral disease, which accounted for only seven ears operated on in this study. There were 80 males and 45 females.

The diagnosis of cholesteatoma usually was made

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TABLE 1. CLINICAL PROFILE OF PATIENTS

Symptoms	
Hearing loss	85%
Otorrhea	73%
Otalgia	32%
Nasal obstruction	26%
Tinnitus	8%
Vertigo	8%
Signs	
Site of cholesteatoma	
Posterior epitympanum	65%
Anterior epitympanum	61%
Antrum	48%
Sinus tympani	35%
Eustachian tube	20%
Petrous apex	1%
Retraction pockets	
Posterior superior quadrant	32%
Attic	20%
Entire membrane	3%
Perforations	
Marginal	10%
Total or subtotal	9%
Posterior central	4%
Anterior central	4%
Other	
Granulation	31%
Mass behind intact tympanic membrane	31%

by an otolaryngologist rather than a pediatrician or general practitioner. The majority of the patients first experienced ear problems before they were 4 years of age. Interestingly, the mothers of a third of the patients had problems during pregnancy, and a family history of ear disease was elicited in about half the subjects. Nonotologic congenital malformations were present in 13% of the children, and a cleft palate in 5%.

The most common presenting symptoms (Table 1) were hearing loss, otorrhea, otalgia, nasal obstruction, tinnitus, and vertigo. Only one patient presented with an intracranial complication (0.8%). Almost all the children (91%) had a history of otitis media, and two thirds had been treated for middle ear effusions. However, only 38% of these subjects had had an adenoidectomy with or without tonsillectomy. Less than half the children (48%) had had myringotomies. Pressure equalization tubes had been inserted once in 42%, while multiple tube insertions had been done in only 19% of the subjects.

Examination of the ear revealed a variety of abnormalities. The presence of retraction pockets, either in the eardrum or extending toward the mastoid, was the commonest finding: they were present in slightly more than half the patients. Granulation tissue was observed in about a third. A similar number were observed to have a whitish mass behind the eardrum. Approximately a quarter of the patients had tympanic membrane perforations.

The cholesteatomas encountered in this series of patients were subdivided into four categories. Forty-eight percent of the patients had primary acquired cholesteatoma with a skin-lined retraction pocket within which keratin debris had accumulated, eroding adjacent bone. Twenty-four percent had congenital cholesteatomas, presenting with a discrete mass behind an intact tympanic membrane, never having had ear drainage or perforated eardrums; on x-ray examination, they had pneumatized mastoids. Ten percent had secondary acquired cholesteatomas in which skin grew through a tympanic membrane perforation into the middle ear and mastoid. The remaining 18% had already had unsuccessful surgery, and consequently it was not possible to classify the original type of cholesteatoma accurately. This last group was composed of 22 patients, eight of whom presented with recurrent disease and 14 with residual disease.

The type of operative approach generally was decided intraoperatively based on the extent of disease, the pneumatization and size of the mastoid, and a clinical assessment of eustachian tube function. The indicators of good eustachian tube function were a well-aerated middle ear space, normal-appearing middle ear mucosa, and a well-pneumatized mastoid.

A tympanotomy approach was selected for patients who had small cholesteatomas localized to the middle ear space (17.2%). This procedure was frequently satisfactory for the removal of congenital cholesteatomas. A canal wall up mastoidectomy was performed in situations in which 1) the approach permitted sufficient exposure to remove the cholesteatoma completely and 2) the function of the eustachian tube was normal enough to aerate the epitympanum and mastoid. Thirty-nine patients (30.5%) had either a posterior facial recess tympanomastoidectomy (ten patients), an atticotomy (16 patients), or an atticotomy with mastoidectomy (13 patients). The most commonly performed procedure was a canal wall down mastoidectomy (52.3%), which allowed optimal exposure of the disease site and eliminated the need to aerate the mastoid.

The destructive properties of cholesteatoma were evident at surgery. The ossicles were most vulnerable: erosion of the long process of the incus occurred most frequently (46%), followed by destruction of the stapes arch (40%) and involvement of the malleus (25%). The facial nerve's bony covering was eroded in 11% of the cases, involving the horizontal portion in all but a single case in which the vertical portion was exposed. However, neither the disease nor the surgery to eradicate it produced facial nerve weakness or paralysis.

Exposure of adjacent brain structures occurred in 11 patients (8%), with eight patients having erosion of the tegmen and three having uncapping of the lateral sinus. One patient in the series had a posterior fossa abscess, and none had thrombosis or phlebitis of the dural sinuses. Fistula of the lateral semicircular canal was observed in two cases (1.6%).

Eradication of the cholesteatoma was considered complete in 97.5% of the cases, and accordingly these were treated using a closed technique. In the remaining three cases, in which matrix could not be removed completely, the questionable area was not grafted, but rather was exteriorized. In 10% of the cases, the cholesteatoma could be removed simply by elevating a tympanomeatal flap that then could be replaced, eliminating the need for a graft. Consequently, 88% of the ears were grafted using temporalis fascia, the adjacent areolar connective tissue layer, and/or tragal perichondrium.

Fifty-seven percent of the patients had primary ossicular reconstructions. Autograft cartilage generally obtained from the floor of the ear canal (45%) or an autograft ossicle (45%) was positioned on the ossicular remnant to reconstruct the sound transmission mechanism. Infrequently, alloplastic total or partial ossicular replacement prostheses were used.

A type III tympanoplasty in which the stapes arch was present was the most commonly encountered situation (33%); followed by type IV (footplate present, 19%); type I (intact ossicular mechanism, 14%); and type II (missing malleus handle with an intact incus, 5%). The remaining 29% were considered a miscellaneous group: 8% had congenital cholesteatoma requiring neither ossicular nor eardrum reconstruction, 18.5% had an eardrum graft without an ossicular reconstruction, and 2.5% had the cholesteatoma exteriorized without middle ear reconstruction.

In chronically diseased ears, the middle ear promontory frequently becomes lined either by squamous epithelium or irreversibly diseased hyperplastic mucosa and therefore has to be removed. Medium thick Silastic sheeting (0.25 mm) was used in 60% of the cases to reconstruct the middle ear cleft and aerate the middle ear. The sheeting was placed into the eustachian tube orifice and was shaped to fit into the middle ear cleft and, in canal wall up procedures, into the epitympanum and mastoid. Thin Silastic sheeting (0.125 mm) was inserted in 18% of the cases to try to prevent the formation of adhesions from a localized area of denuded promontory to the grafted eardrum.

Ninety percent of the patients were followed for at least 1 year. Seventy percent were followed for up to 2 years, 59% up to 3 years, and 36% for 5 years or longer. The average clinical follow-up was 3.9 years, with the range being from 3 months to 13.5 years. Ten patients (8%) have had residual disease, while only four (3%) have developed recurrent cholesteatoma. Additionally, one patient had stenosis of the external auditory canal that required corrective surgery. Postoperatively, otorrhea recurred in ten of the ears (8%). Three of the patients with draining ears had residual cholesteatoma, and one had recurrent cholesteatoma. The grafts remained intact in 92%, with 2% of these patients having lateralization of the graft. Eight percent of the patients developed small perforations.

TABLE 2. EFFECT OF SURGERY ON SPEECH RECEPTION THRESHOLD (SRT)

	Postop SRT > 30 dB (55%)	*Postop SRT ≤30 dB (45%)*
Preop SRT >30 dB, 62% (n = 76)	Hearing unrestored (56/76) 74%	Hearing restored (20/76) 26%
Preop SRT ≤30 dB, 38% (n = 46)	Hearing impaired (11/46) 24%	Hearing maintained (35/46) 76%

Staged surgery was preplanned in 11 cases (9%); in one case to provide a second look, and in ten cases for ossicular reconstruction. However, to date only four of this latter group have had the second operation.

AUDIOLOGIC RESULTS

Overall Group. The primary auditory goals for these patients with cholesteatoma were to preserve hearing when it was normal and, when a loss was present, to restore it to a functional level. A speech reception threshold (SRT) of 30 dB was chosen as the standard for serviceable hearing. In order to evaluate treatment results, preoperative and postoperative SRTs were compared. A total of 122 patients were used for this analysis, since three patients had to be dropped because of a lack of accurate preoperative data.

Overall, in the entire series a hearing improvement of only 1.5 dB was observed. Postoperatively, serviceable hearing was attained in 45% of the patients. The remaining 55% had SRTs over 30 dB (Table 2). When assessing the patient's ability to function, it should be taken into account that these results reflect the hearing of the affected operated ear. Consequently, given the relative paucity of bilateral cases (5.4%), a much larger number of patients had overall serviceable hearing. In addition, in those cases followed for 3 years or more the hearing improvement was maintained.

Ossicular Reconstruction. A subgroup that consisted of 67 patients who had primary ossicular reconstruction was analyzed. Patients in whom a reconstruction was not performed either because the transducer mechanism was intact or because the reconstruction was staged were omitted from this analysis.

An overall average hearing improvement of 3 dB pure tone average (PTA) was observed. Postoperatively, serviceable hearing (≤30 dB) was attained in 48% of the patients in this group.

Four categories of hearing levels were established,

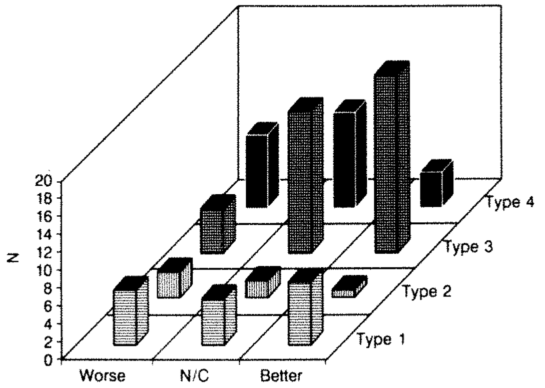

Fig 1. Change in SRT by tympanoplasty type.

which correlate with those used by the senior author in a previous study[1] on cholesteatoma:

1. Hearing restored: 33%. Fourteen of the 42 patients with a preoperative SRT worse than 30 dB achieved an SRT of equal to or better than 30 dB after surgery.
2. Hearing unrestored: 67%. Twenty-eight of these 42 patients who had poor hearing prior to surgery continued to have nonserviceable hearing after reconstruction.
3. Hearing maintained: 72%. Eighteen of the 25 patients with good hearing preoperatively maintained an SRT of equal to or better than 30 dB.
4. Hearing impaired: 28%. Seven of the 25 children who had serviceable hearing preoperatively experienced a deterioration so that their SRT was worse than 30 dB following surgery.

The discrimination score was unchanged in 90% of the patients in this group. The other 10% experienced an improvement of at least 12% in their scores. No patient showed greater than a 12% loss. In this group, the following residual air-bone gaps were observed following reconstruction: 0 to 10 dB, 20% of patients; 0 to 20 dB, 38%; 0 to 30 dB, 57%.

The result of the various ossicular reconstructions revealed that there was no appreciable change in SRTs among the six patients with an absent malleus but an intact incus-stapes complex who had a type II tympanoplasty (Fig 1). The results of reconstruction when the stapes arch was present and a type III tympanoplasty was performed were reviewed. Of the 41 patients who underwent a type III tympanoplasty, 23 exhibited unchanged SRTs. However, 15 patients showed at least a 10-dB improvement in their SRTs, while only three experienced a significant deterioration. Finally, most of the 23 patients with an absent stapes arch who had a type IV tympanoplasty showed little change in their SRTs (three of these patients were excluded from the initial analysis in this section because of incomplete audiologic data).

Canal Wall Up Versus Canal Wall Down. The hearing results were reviewed for the three operative groups: tympanotomy, canal wall down, and canal wall up. The audiologic data were evaluated based on preoperative and postoperative SRTs. The first group, which was composed of those patients who had tympanotomies, experienced a small, insignificant average loss of 0.7 dB SRT after surgery. The second group, which was composed of those who underwent canal wall down mastoidectomies, demonstrated an average improvement in SRT of 3.2 dB. Finally, the third group, which included those patients who underwent some form of canal wall up mastoidectomy, demonstrated basically no change in hearing (Fig 2). In summary, only those patients who had a canal wall down procedure and a type III tympanoplasty had a significant chance of having a hearing improvement postoperatively (χ^2 test, $p<.05$).

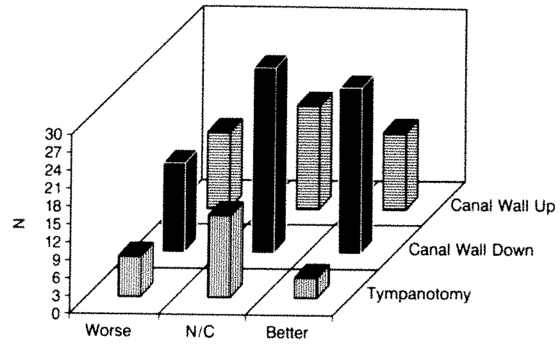

Fig 2. Change in SRT by mastoidectomy type.

Bone Conduction. One of the questions posed with respect to tympanomastoid surgery performed on children is whether the surgical manipulation of the middle ear structure will have a permanent deleterious effect on bone conduction. This issue was evaluated using 4 kHz as an indicator. Ninety-seven cases were reviewed. In general, there was no difference between the preoperative bone conduction at 4 kHz and the postoperative result. With a variability of ±10 dB, 78 patients showed no change, nine were worse, and ten were better. A similar analysis was done using PTA in which the thresholds at 500, 1,000, and 2,000 Hz were averaged for bone conduction. With a variability of ±10 dB, 88 patients showed no change, six were worse, and three were better. One patient in the series developed a progressive neurosensory deterioration postoperatively that resulted in a profound neurosensory loss.

Age. Since the patients in this study ranged from 2 to 18 years of age, an analysis was made comparing the audiometric values obtained in the younger patients with those of the older patients to determine if any age group had better results or if there was any age-related bias. The results indicated that the patients over 6 years of age had better audiologic results than younger patients. However, patients over 11 years of age had no statistically significant difference in hearing versus those under that age.

The youngest (2 to 3 years of age) and oldest (17 to 18 years of age) patients did not have results that biased the data.

CLINICAL CORRELATIONS AND RESULTS

The incidence of residual and recurrent disease is the primary indicator of success in cholesteatoma surgery. Residual cholesteatoma is defined as keratinizing squamous epithelium that was not completely removed and resulted in regrowth of the cholesteatoma. Recurrent cholesteatoma is defined as disease that redevelops because middle ear and/or mastoid ventilation could not be established successfully at the initial procedure. Consequently, in recurrent cholesteatoma a retraction recurs that accumulates keratin and enlarges, thereby invading the mastoid and/or sinus tympani.

In the 127 ears operated upon, residual disease occurred in ten cases (8%) and recurrent disease in four cases (3%). The largest number of cases of residual disease[6] were associated with canal wall down procedures. However, there were also two cases of residual disease following a canal wall up atticotomy and two cases following middle ear exploration for removal of congenital cholesteatoma. Only patients who had canal wall up procedures developed recurrent disease. There were two cases of recurrent disease in patients who underwent a facial recess approach, one case in a patient who had undergone an atticotomy with mastoidectomy, and another in a patient who had an atticotomy alone. Most of the patients who had residual or recurrent disease were over 6 years of age.

The average length of time postoperatively until a recurrence was found was 3.5 years. The range was 8 months to 6 years. The average length of time postoperatively until a residual cholesteatoma was found was 1.5 years. The range was 9 months to 3 years. Postoperatively, residual disease was observed only in the middle ear. The most common site for recurrent disease was the mastoid, with only one case also involving the middle ear. Residual disease was most likely to occur in patients who had some form of preoperative retraction of the tympanic membrane (six of eight patients). Perforation played an insignificant role.

DISCUSSION

The treatment of cholesteatoma in children poses special problems for the otologist who must provide a disease-free ear that will remain stable throughout adulthood while maintaining serviceable hearing, which is essential for the development of normal language and communication skills.

The diagnosis of cholesteatoma in children is often difficult. In general, many children are diagnosed incorrectly because of a paucity of symptoms; their uncooperativeness, which makes examination difficult; and their small, tortuous ear canals. Indeed, in this series, on physical examination only 55% of the patients had a retraction pocket, 31% had granulation tissue in the ear, and 27% had a perforation. Additionally, most of the patients had a hearing loss and a history of otorrhea. Consequently, in children, the triad of otorrhea, hearing loss, and abnormal otoscopic findings should raise the possibility of cholesteatoma.

The presence of congenital growths poses another challenge in the diagnosis of pediatric cholesteatoma.[9] In our series, 31% of patients presented with a mass behind the intact eardrum. Most of these cases represented congenital cholesteatomas. The growth patterns of congenital and acquired cholesteatoma are different. Congenital cholesteatomas tend to originate in the anterior middle ear and may expand into the anterior epitympanum and, over time, into the petrous apex without producing any symptoms. In contrast, acquired cholesteatomas arise from middle ear structures and extend into the posterior or anterior epitympanum and into the antrum, commonly producing significant otologic symptoms. Perhaps a failure to distinguish between these two types of cholesteatoma has obscured a full understanding of this disease in children. It is also possible that our high incidence of congenital disease could have been due to the referral nature of the senior author's practice.

A major area of disagreement among the authors who have studied cholesteatoma in children is the question of what age groups qualify as pediatric patients. Glasscock et al,[3] Wullstein,[10] and Goodey and Smyth[11] use age 16 as a cutoff, Abramson et al[12] use age 9, and Palva et al[2] subdivide childhood into three groups (0 to 5, 6 to 10, and 11 to 15 years of age). In this series the patients ranged in age from 2 to 18 years, a designation used on the recommendation of the Department of Pediatrics at Mount Sinai Hospital. The inclusion of 17- and 18-year-olds in our study did not significantly affect any of the analyses. However, an analysis of our results did confirm previous findings that children under 6 years of age tend to perform worse than older ones. The reason for this is not clear. Perhaps older children are better able to verbalize their ear complaints or may undergo more effective screening in school and, therefore, are diagnosed earlier in the course of the disease process. Age did not bias our selection of a surgical approach.

Most authors agree that cholesteatoma in children is more aggressive and undergoes faster growth than in adults. Ruedi[13] suggests that there is a connective tissue layer in the mastoid of young children that helps to promote cholesteatomatous matrix growth. Similarly, the growth of the mastoid and the surrounding cranium may have some effect on the growth factor in cholesteatoma. Our results in this study confirmed the aggressive nature of pedi-

TABLE 3. SURGICAL TREATMENT

Study	*Treatment Type*
Palva et al[2]	CWD mastoidectomy
Glasscock et al[3]	CWU mastoidectomy
Jahnke[4]	CWD mastoidectomy
Tos[5]	41% CWU; 37% CWD; 12% tymp
Sheehy[6]	CWU mastoidectomy
Jansen[7]	CWU mastoidectomy
Smyth[8]	CWU/CWD mastoidectomy
This study	52% CWD; 30% CWU; 17% tymp

CWU — canal wall up, CWD — canal wall down, tymp — tympanotomy.

TABLE 4. RATES OF RECURRENT AND RESIDUAL DISEASE

Study	*N*	*Recurrent*	*Residual*
Palva et al[2]	65 pts	—	5%
Glasscock et al[3]	43 ears	23.0%	23%
Jahnke[4]	117 ears	8.5%	—
Tos[5]	122 pts	12.0%	—
Sheehy[6]	181 pts	—	51%
Jansen[7]	313 pts	—	8%
Smyth[8]	79 pts	8.0%	—
This study	127 ears	3.0%	8%

atric cholesteatoma. The growth of cholesteatoma in the middle ear frequently tended to involve the ossicles in high numbers: the incus, 79%; the malleus, 61%; and the stapes, 38%. Jahnke,[4] Tos,[5] and Palva et al[2] agree with this point in contrast to Armstrong,[14] who stated that cholesteatoma involved the ossicles less frequently in children. However, when compared to cholesteatoma in adults, fistulas of the semicircular canals, facial paralysis, and intracranial complications occurred less often in the pediatric group. Tos[5] and Palva et al[2] reported no labyrinthine fistulas, and in this review a 1% incidence was observed.

Perhaps the area of greatest disagreement among otologists relates to the choice of surgical approach (Table 3).[2-8] In this series, the surgical procedure selected was individualized, taking into account several factors: the location and extent of the disease, the clinical assessment of eustachian tube function, the mastoid size and pneumatization, and the degree of involvement of the ossicles. The functional status of the eustachian tube was estimated indirectly by the appearance of the middle ear mucosa, the status of the middle ear space, the condition of the pars tensa, the pneumatization of the mastoid bone, impedance audiometry, and the presence of either nasal obstruction or adenoidal hypertrophy. However, the age of the patient did not influence the selection of the surgical approach.

The patients who had congenital cholesteatoma generally had localized disease and underwent some form of closed procedure. Most of these patients had only a tympanotomy and no mastoidectomy. Patients with extensive cholesteatoma, poor eustachian tube function, and sclerotic mastoids generally were treated with canal wall down mastoidectomies. A canal wall up approach was used on about 30% of the patients. These patients generally had localized disease and clinically seemed to have adequate eustachian tube function. In almost all cases, the grafting of the middle ears and mastoid cavities was successful, and there were few instances of chronic otorrhea.

Most of the patients underwent a primary reconstruction of the ossicular mechanism. Modest hearing improvements were observed, the best results being achieved by type III tympanoplasty with autograft cartilage or bone placed on the stapes capitulum. In those cases in which it was assessed that the results of ossicular reconstruction would be poor as evidenced by extensive disease, poor eustachian tube function, no middle ear space, a long history of middle ear effusions, or a history of adenoiditis, the reconstruction was staged. In these cases, the eardrum was grafted and Silastic was used to restore the middle ear space, but the ossicular repair was deferred to a second stage. A "second look" procedure was needed infrequently, since serial computed tomography was felt to be effective in detecting residual disease.

The rate of residual disease or recurrence experienced by the patients in this study is comparable to that of other studies of cholesteatoma. For example, the 3% recurrence and 8% residual disease rates reported in this study are comparable to those reported by the senior author in a 1982 study,[1] which included both adult and pediatric cases. These results were comparable to those reported by Tos,[5] who reported a low recurrence rate (2%) and a 10% rate of residual disease. Other authors, however, have noted higher failure rates among pediatric patients. Sheehy,[6] for example, reported as high as a 51% residual disease rate, while Glasscock et al[3] reported both a 23% residual disease rate and a 23% recurrence rate. Perhaps our low failure rate is due to a philosophy of treating each cholesteatoma individually, selecting the most appropriate procedure that will assure the eradication of the disease completely, and keeping all surgical techniques in our operating armamentarium. In contrast, Sheehy[6] and Glasscock et al[3] primarily used a single surgical approach, which may explain their high failure rates (Table 4).[2-8]

In treating children with cholesteatoma, the hearing results take on a great importance. Fortunately, most of the patients in this study had unilateral disease with serviceable hearing in the opposite ear. Only one patient showed a profound loss of hearing after surgery. In general, the patients who had good hearing preoperatively tended to maintain their hearing after surgery, while those patients who had poor hearing preoperatively had only slight improvements. Further work needs to be done on developing ways to achieve improved hearing results after cholesteatoma surgery.

This study demonstrates that successful treatment of cholesteatoma in children can be accomplished by employing the same basic principles of treatment used for cholesteatoma in adults.

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FOURTH NATIONAL TRAUMATIC BRAIN INJURY SYMPOSIUM

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CHOLESTEATOMA SURGERY: CANAL WALL DOWN PROCEDURES

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We prefer the intact canal wall technique for tympanoplasty with mastoidectomy, but use a canal wall down procedure in up to 25% of cases. Creating a round cavity with a large meatus is imperative if one is to obtain a trouble-free ear. The five types of canal wall down procedures are defined, as are our indications for using them. Results in 19 only hearing ears and 19 labyrinthine fistula cases are presented, along with 64 tympanoplasty cases.

KEY WORDS — cholesteatoma, labyrinthine fistula, mastoidectomy, meatoplasty, tympanoplasty.

At the Otologic Medical Group (OMG) we prefer the intact canal wall technique in the management of aural cholesteatoma, but use various canal wall down (CWD) procedures in up to 25% of cases.

The purposes of this paper are to clarify the types of mastoidectomy, to review the important points in creating a trouble-free cavity, to discuss our indications for using a CWD technique, and to present the results in 103 primary cases. Nineteen had a labyrinthine fistula, and 19 were in only hearing ears.

TYPES OF CHOLESTEATOMA SURGERY

Prior to the introduction of tympanoplasty in the mid-1950s, mastoid cholesteatoma was managed by one of two classic operations: modified radical mastoidectomy or radical mastoidectomy. The object was to exteriorize the disease and preserve hearing if possible.

When Wullstein[1] and Zollner[2] introduced tympanoplasty with mastoidectomy, it was a CWD procedure. In the early 1960s, many began to use the intact canal wall technique,[3] and a terminology problem developed. To clarify the terminology, a committee of otologists was organized in 1962 under the direction of David Austin, MD. The committee's recommendations were presented to the Committee on Conservation of Hearing of the American Academy of Otolaryngology, and a report was published by the Committee in 1965.[4] This report was on terminology for all operations for chronic otitis media. Here, I will discuss only terminology for those procedures involving mastoidectomy.

Tympanoplasty With Mastoidectomy. Tympanoplasty with mastoidectomy is an operation to eradicate disease in both the mastoid process and middle ear cavity and to reconstruct the middle ear conducting mechanism. There are three technical variations, the first two of which are CWD procedures.

1. Open cavity technique — creation of a permanently exteriorized mastoid cavity
2. Obliteration technique — creation of a mastoid cavity followed by cavity obliteration
3. Intact canal wall technique (canal wall up, posterior tympanotomy, or combined approach techniques) — technique in which the exenterated mastoid cavity is not exteriorized to the external auditory canal

Radical Mastoidectomy. Radical mastoidectomy is an operation performed to eradicate middle ear and mastoid disease in which the mastoid cavity, epitympanum, middle ear, and external auditory canal are converted into a common cavity exteriorized through the external meatus. (It does not involve grafting or reconstructive procedures, and the tympanic membrane and ossicular remnants, with the exception of the stapes, are removed.)

Modified Radical Mastoidectomy. Modified radical mastoidectomy is an operation performed to eradicate mastoid disease in which the mastoid cavity, epitympanum, and external auditory canal are converted into a common cavity exteriorized through the external meatus. (This differs from the radical mastoidectomy in that the tympanic membrane, or remnants thereof, and ossicular remnants are retained to preserve hearing. No grafting or reconstructive procedure is involved. One may, furthermore, retain some of the cholesteatoma matrix to help seal the middle ear and line the epitympanum.)

Mastoid Obliteration Operation. The mastoid obliteration operation is an operation to eradicate disease and to obliterate a mastoid or fenestration cavity.

Comment. The main problem in terminology involves the modified radical mastoidectomy. Although this is a classic operation, not involving tympanic membrane grafting or ossicular reconstruc-

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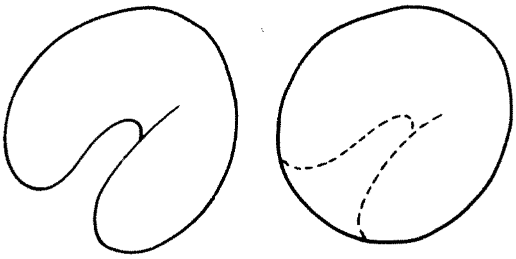

Fig 1. Diagram of bean-shaped cavity (left) and round cavity (right) created by lowering posterior canal (facial ridge) wall to level of floor of ear canal.

tion, this is not well understood. Many have been taught, incorrectly, to use the term modified radical with tympanoplasty to describe a tympanoplasty with mastoidectomy in which the canal wall is taken down.

CREATION OF A TROUBLE-FREE CAVITY

The key to success in otologic surgery is not whose technique or what technique one uses, but how well one uses it and one's own ability and judgment. If principles are followed, a CWD operation should result in a trouble-free ear, often one that requires little care. A CWD tympanoplasty yields hearing results comparable to those from an intact canal wall tympanoplasty in our hands.

There are four principles: 1) create a round cavity, 2) create an adequate-sized meatus, 3) saucerize the cavity margins, and 4) amputate the mastoid tip when indicated.[5,6] Lowering the posterior canal wall to create a round cavity and creating a large meatus are the most important.

To create a round cavity, the posterior canal wall should be taken down to the level of the floor of the external canal, or the facial nerve, whichever is encountered first. Fear of damaging the facial nerve, or being uncertain where it is, is probably the most common reason for leaving the posterior canal wall (facial ridge) high. This results in a bean-shaped cavity rather than a round cavity, a cavity in which there are areas difficult to see and clean and areas that trap moisture (Fig 1).

There is no harm in having a meatus larger than necessary, so one should err on this side. The larger the meatus, the less likely one is to have a cavity problem, even if the other principles are not followed. We enlarge the meatus by making a horizontal (posterior-to-anterior) incision in the cavum conchae, through the skin, cartilage, and postauricular soft tissue, and then remove the underlying cartilage (Fig 2A). This results in a triangle-shaped meatus (Fig 2B). The meatus is packed with Xeroform (or Adaptic) gauze, which is left in place for up to 3 weeks if the ear does not suppurate.

If one saucerizes or rounds off the cavity margins above, behind, and below, the replaced auricle and soft tissue assume a more medial position during healing. The end result is a smaller cavity.

Amputation of the mastoid tip is an additional method of reducing cavity size in those cases in which it is necessary to create or revise a cavity in a well-developed mastoid. Amputating the tip also eliminates a dependent cavity area that is not visible, regardless of how large a meatus is created (Fig 3).

THE STUDY

In 1984 I reviewed the records of the OMG's patients with chronic otitis media who had had cavities created at initial operations from 1974 through 1981. Table 1 shows the procedures used during these 8 years, the majority of which were intact canal wall tympanoplasties with mastoidectomy. There were 103 CWD operations, representing 12.4% of the primary mastoid surgery for cholesteatoma during the 8 years. Two thirds of these CWD operations were performed by the author.

Six months or more follow-up was available on 95% of patients. Follow-up at 1 year was 90%, and

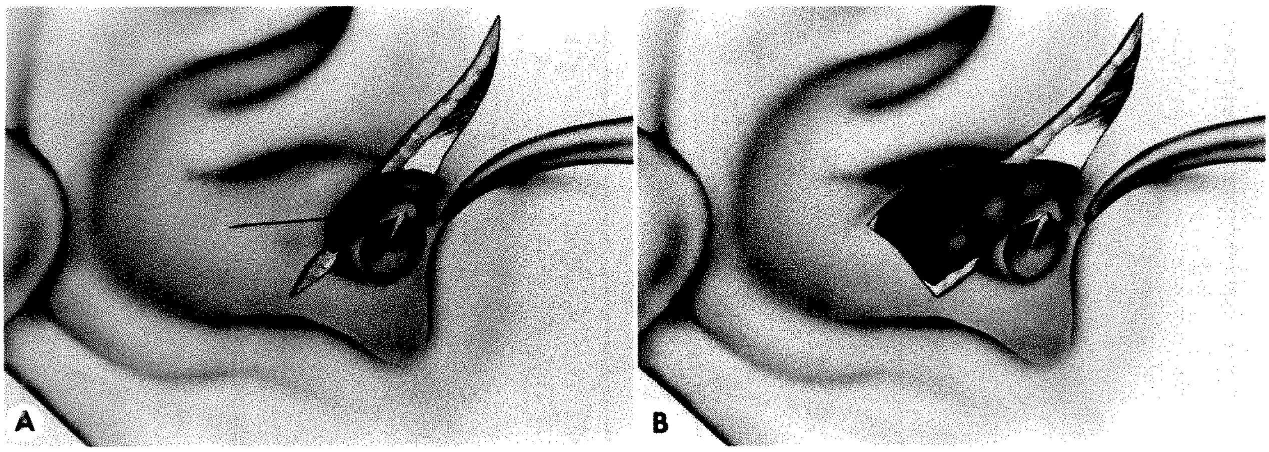

Fig 2. Meatoplasty. A) Initial steps. Number two endaural incision (paralleling crus helicis) serves as relaxing incision. Small posteroinferior incision across edge of cavum conchae serves similar purpose. Horizontal incision is made through skin, cartilage, and postauricular soft tissue of cavum conchae. B) Final appearance. Cartilage and soft tissue have been removed (postauricularly) to allow two skin flaps to fold into cavity without tension.

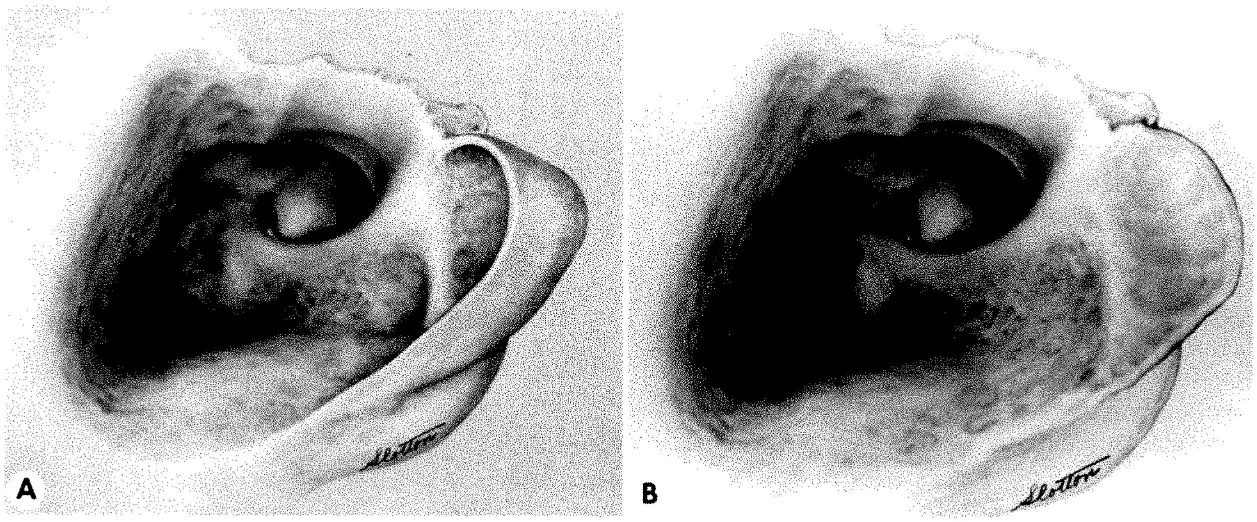

Fig 3. Temporal bone dissection to demonstrate radical mastoidectomy in well-pneumatized mastoid. A) Large mastoid tip is shown. B) Mastoid tip cortex has been removed anteriorly, laterally, inferiorly, and posteriorly, leaving only medial plate. Soft tissue of tip and neck fall into and obliterate tip area.

at 2 years, 75%. Forty percent had 4 years or more follow-up.

Table 2 shows that we are less likely to perform CWD surgery in children and more likely to use this technique in those 66 years of age or older.

Preoperative complications of cholesteatoma are not common.[7] When they are present, we are more likely to use a CWD procedure (Table 2).

INDICATIONS FOR CANAL WALL DOWN SURGERY

Discussing the indications for a CWD procedure may be of only academic interest to those who believe that this is the best way of managing cholesteatoma cases requiring mastoidectomy; but for those who prefer, as we do, to use the intact canal wall technique whenever possible, this discussion should be of interest.

The decision to use a CWD technique may be made preoperatively, but more often than not, the operation is begun as an intact canal wall procedure and the decision to exteriorize the mastoid is made intraoperatively.

Preoperative Decision. The decision to perform a CWD procedure is made preoperatively in some cases. This decision is based on consideration of the hearing in the involved ear, the status of the opposite ear, preoperative complications, the degree of posterior canal wall destruction, and the age and health of the patient.

TABLE 1. MASTOID SURGERY FOR CHOLESTEATOMA (1974-1981)

Total OMG Procedures (N = 828)		*Percent*
Intact canal wall tympanoplasty/ mastoidectomy		87.6
Canal wall down surgery		12.4
Tympanoplasty with mastoidectomy		
With cavity obliteration	7.3	
Cavity left open	0.5	
Classic modified radical or radical mastoidectomy	4.5	
Total obliteration of cavity and ear canal	1 case	

With rare exceptions, a cholesteatoma requiring mastoid surgery in an only hearing ear is managed by a CWD technique, and this was the indication in 19 cases (Table 2). Usually, the procedure is a classic modified radical mastoidectomy, leaving the middle ear and hearing the way they were. We also may use the classic modified radical procedure in cases in which the affected ear has serviceable hearing and the opposite ear has a severe uncorrectable impairment. We do not wish to jeopardize the only serviceable ear.

In labyrinthine fistula cases, we may decide preoperatively to use a CWD operation if the mastoid is small or if the opposite ear has cholesteatoma that will require surgery. If the hearing is serviceable, we may perform a classic modified radical procedure, particularly in those in poor health or in the elderly.

TABLE 2. CHOLESTEATOMA SURGERY: PATIENT CHARACTERISTICS (1974-1981)

	CWD (N = 103)	*All Cases (N = 828)*
Age of patient (yr)		
15 or less	11%	18%
16 to 65	80%	78%
66 or more	9%	4%
Preoperative complications		
Fistula	18%	4%
Facial paralysis	4%	1%
Dead ear	5%	1%
Indications for canal wall down procedure		
Small mastoid	44%	
Canal destruction	22%	
Only hearing ear	19%	
Other factors	15%	

TABLE 3. PRIMARY CANAL WALL DOWN SURGERY (1974-1981)

CWD Procedures (N = 103)		*Percent*
Tympanoplasty with mastoidectomy		62
Cavity obliteration	58	
Open cavity	4	
Modified radical mastoidectomy		29
Radical mastoidectomy		8
Total obliteration of cavity and ear canal		1

A CWD operation may be decided on preoperatively if it can be seen that the cholesteatoma has destroyed a significant portion of the posterior canal wall. If the opposite ear already has a cavity, we may elect to create a cavity. In elderly patients, or in those in poor health, we are more likely to use the classic modified radical mastoidectomy.

Intraoperative Decision. We prefer the intact canal wall technique for cholesteatoma surgery, mainly because we would prefer not to create a cavity unnecessarily. Hence, with the exceptions mentioned above, we begin surgery with that intention.

When we encounter a very contracted mastoid, particularly with an ear canal slanting forward and upward, or encounter unsuspected canal wall destruction, we do not hesitate to take the canal wall down. In two thirds of the cases, these were the indications (Table 2).

OPERATIVE PROCEDURES

Table 3 shows the distribution of CWD cases.

Tympanoplasty Cases. Sixty-four of the 103 CWD cases were tympanoplasties with mastoidectomy.

At OMG we use the lateral surface (onlay) grafting technique 98% of the time.[5] In CWD tympanoplasty we are more likely to use the undersurface technique, and did so in seven of 64 (11%). These patients did well. Two of the lateral surface grafts failed.

Only 40% of the 64 tympanoplasties were managed by a one-stage procedure. Eighty-five percent of patients with 6 months or more follow-up had a 20-dB or less postoperative conductive deficit. A block of tragal cartilage, placed on the stapes capitulum, was used in most cases.

Of the 38 cases managed in two stages (because of absent mucosa), 24 had been revised and had follow-up. Most had a total ossicular replacement prosthesis to the footplate, with cartilage placed between the platform and the tympanic membrane. Seventy-five percent of patients had a 20-dB or less residual conductive deficit.

There was one total loss of hearing, an iatrogenic lateral canal fistula (author's case).

Modified Radical Mastoidectomy. Classic modified radical mastoidectomies were performed on 30 of the 103 ears. Almost all were planned preoperatively. Two were on elderly patients (73 and 79 years of age) and one was on a child (7 years of age).

Fifteen of the modified radical mastoidectomies were on only hearing ears, three others were on ears with labyrinthine fistulas, and three were on better-hearing or normal-hearing ears of patients in whom prior surgery on the opposite ear had resulted in a cavity.

There was no follow-up on two ears (in patients from out of the country), and five had no hearing preoperatively. Twenty of the 23 ears had the same or better hearing, two were worse by air conduction, and one developed a 30-dB sensorineural impairment.

Radical Mastoidectomy. A classic radical mastoidectomy was performed on eight ears. Three were in children (3, 11, and 12 years old) who had diffuse cholesteatosis and a totally destroyed middle ear. One adult (with an only hearing ear) had an epidural abscess and meningitis.

Three ears had no hearing preoperatively. Three with hearing remained at the preoperative level, and two were worse by air conduction. There were no postoperative sensorineural impairments.

Mastoid Obliteration Operation. Although the mastoid cavity was obliterated in a number of the tympanoplasty cases, the surgery was limited to a mastoid obliteration operation in one case. This was a total obliteration of the mastoid, middle ear, and external auditory canal.[8]

The total obliteration procedure was performed on an ear that was badly draining and functionless preoperatively and had canal wall destruction by the cholesteatoma. The surgeon (Dr John House) was certain of cholesteatoma removal and obtained a dry, healed ear.

Cavity Healing. We prefer the intact canal wall procedure over CWD procedures for cholesteatoma surgery because of the more rapid healing, the lack of need for water precautions, and the lack of need for periodic cavity cleaning.

Ninety-two of 98 cavities with 6 months or more follow-up eventually healed. Two thirds were healed in 4 months (compared to 98% of intact canal wall cases healed in 4 months). Seven ears required 7 months or more to heal.

ONLY HEARING EARS

Nineteen of the CWD operations were performed on only hearing ears, two of which also had a labyrinthine fistula. A radical mastoidectomy was performed in one case, a classic modified radical mastoidectomy in 15 cases, and a one-stage CWD tympanoplasty with mastoidectomy in three cases.

There was no follow-up in two foreign patients. The hearing remained at its preoperative level in 12 of 17 patients with follow-up, was better by 10 dB or more in two, and was worse by air conduction in three. There were no sensorineural impairments.

FISTULA CASES

Management of the labyrinthine fistula was the subject of a 1979 paper.[9] Ninety-seven fistulas were encountered in 1,028 operations during the 10 years preceding 1974. Canal wall down procedures were performed in 42%. Since 1974, the incidence of labyrinthine fistula in our practice has decreased to 4% (33 of 828), but we managed 60% with CWD procedures.

A lateral canal fistula was present in 19 of the 103 cases. Two were in only hearing ears, two were in patients with preoperative facial nerve paralysis, and five were in ears with no hearing preoperatively.

Nine patients (including the two with only hearing ears) were managed with modified radical mastoidectomies. In ten, CWD tympanoplasties were performed, leaving the matrix over the fistula. There were no postoperative sensorineural hearing impairments.

DISCUSSION

A number of questions may well have developed in the reader's mind by this time. If the results of CWD tympanoplasty are good, why use what some consider the more difficult intact canal wall technique? What are our indications for CWD surgery? Have these indications, and the percentage of cases so managed, changed in the last 10 years? In answering these questions, I hope that those who routinely use CWD procedures will better understand the philosophy of those who do not routinely create a cavity.

Why Not CWD For All Cases? Although we often hear comments from advocates of CWD techniques that their hearing results are not as satisfactory as with the intact canal wall, this has not been our experience. Perhaps this is because our indications for (and incidence of) staging the operation — to obtain an air-containing, mucosa-lined middle ear space — are almost the same for both procedures. And we try to obtain a wide middle ear space in CWD tympanoplasty, rarely, if ever, placing the graft on the capitulum.

It is stated often by advocates of CWD surgery that the operation is quicker, easier, and safer. We find that a CWD tympanoplasty is not easier; in fact, it may be more difficult to perform properly. If we begin the tympanoplasty knowing that we will use a CWD technique, it may require 10% to 20% less time, but it is not easier when properly performed. As far as safety is concerned, this is related to the surgeon's ability, rather than how he handles the canal wall.

We use the intact canal wall technique in preference to CWD tympanoplasty (when there is no contraindication) because we would prefer not to create a cavity, with the limitation of activities it may impose on the patient. Furthermore, if a hearing aid is indicated in the future, it will be easier to fit in a normal canal (and meatus) and may have better sound quality.

Finally, we find that the badly infected ear, especially one with *Pseudomonas* in a developed mastoid, is more likely to have a favorable outcome with the intact canal wall technique. Canal wall down surgery in such cases may well result in continued discharge from a large cavity.

What Are Our Indications For CWD Surgery? Indications (and contraindications) for a surgical technique are rarely absolute. But we almost always use CWD surgery, and usually a classic modified radical mastoidectomy, in only hearing ears with cholesteatoma.

Some have interpreted this as an indication that we believe that CWD surgery is safer; we do not. Our objective in the only hearing ear is to perform just one operation and maintain the hearing, whatever its level. To use the intact canal wall technique, or even routinely to perform a CWD tympanoplasty, in such a case may well require a two-stage procedure to obtain (or maintain) serviceable hearing. This increases the risk of further hearing loss because of multiple operations and manipulation of the ossicular remnants.

Patients with a lateral canal fistula due to cholesteatoma are at risk (5% to 10%) of losing their hearing regardless of what type of procedure is performed. Unless there is a partially developed mastoid in this adverse condition, we usually use a CWD technique. This allows us to leave the matrix over the fistula undisturbed until a decision is reached on how best to manage it.

Little need be said about inadequate exposure (contracted mastoid) or canal wall destruction. But what about the problem of uncertainty of disease removal? If the cholesteatoma extends to areas that are inaccessible, no procedure will result in a truly safe ear. If, on the other hand, all areas are accessible but complete disease removal is not certain, it is reasonable to perform an intact canal wall technique and reexplore the ear in 9 to 12 months for residual cholesteatoma. Residual disease is more common in the middle ear than in the mastoid, and our incidence of middle ear residual disease is the same in CWD procedures as it is in intact canal wall procedures.

Finally, one might ask whether eustachian tube function plays a part in the decision. It rarely does. We do not test eustachian tube function prior to surgery for chronic otitis media; but there are occasional situations in which we can be almost certain that, even with the two-stage procedure, it is unlikely that we could develop an air-containing, mucosa-lined middle ear space. This occurs primarily in cleft palate and Down's syndrome patients with bilateral cholesteatoma. Not only do we use a CWD procedure in such situations, but we usually would perform a classic modified radical mastoidectomy. If the other ear is normal, we assume that eustachian tube function is normal and approach the surgery as in any other case.

Have Our Percentages of CWD Cases Changed? Over the last 30 years, there have indeed been changes in technique. Prior to 1960, the majority of cholesteatoma cases were managed by the CWD procedure. There was a gradual decrease in the number of CWD procedures through the 1960s. Through the 1970s, it was not unusual for our group to use the intact canal wall procedure in 90% of cases in any given year, and that is manifested in this report.

Over the last 5 years, CWD procedures have been performed in 15% to 25% of cases. This is probably not due to any major change in our philosophy or indications, but to referral of problem cases (only hearing ears, fistulas). This explains why I have the highest percentage of CWD procedures (20% to 45%) and performed two thirds of the series reported here.

CONCLUSIONS

1. At the Otologic Medical Group we prefer the intact canal wall technique for cholesteatoma surgery, but currently use canal wall down procedures in up to 25% of our primary operations for cholesteatoma.
2. To obtain a dry, healed, trouble-free ear in canal wall down surgery, it is necessary to create a round cavity with an adequate-sized meatus. It is helpful to saucerize the cavity margins and to amputate the mastoid tip when indicated.
3. Only hearing ears with cholesteatoma are best managed by the classic modified radical mastoidectomy.
4. Hearing results in canal wall down tympanoplasty are the same as in intact canal wall tympanoplasty in our hands. This is because our indications for staging the operation are the same, and we create a wide middle ear space.

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XIV WORLD CONGRESS OF OTORHINOLARYNGOLOGY

The XIV World Congress of Otorhinolaryngology will be held June 11-16, 1989, in Madrid. For further information, contact J. J. Alvarez-Vicent, MD, Secretary General, Villanueva 11, 28001 Madrid, Spain; phone (34) 1 431 26 92.

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POTENTIATION OF OTOTOXICITY BY GLUTATHIONE DEPLETION

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The combination of 10 mg/kg ethacrynic acid (ETA) and 100 mg/kg kanamycin (KA) caused neither morphologic damage to the cochlea nor change in the auditory brain stem response of the chinchilla. However, after pretreatment with a single dose of buthionine sulfoximine (BSO; 800 mg/kg intraperitoneally) to reduce intracellular glutathione (γ-glutamylcysteinylglycine; GSH) levels, the above single administration of ETA and KA resulted in complete deafness and severe morphologic damage. The kidney, which has a rapid GSH turnover and is therefore especially susceptible to GSH depletion by BSO, also demonstrated severe damage after this treatment. A similar rapid turnover of GSH and resulting limited capacity to detoxify reactive metabolites and free radicals may determine cochlear and renal vulnerability to this toxicity. These findings may explain the clinical observations of enhanced ototoxicity in patients administered aminoglycoside antibiotics concomitantly with loop diuretics.

KEY WORDS — cochlea, ethacrynic acid, glutathione, kanamycin, ototoxicity.

INTRODUCTION

One of the most dramatic and least understood phenomena in drug ototoxicity is the profound enhancement of the cochlear toxicity of the loop diuretics such as ethacrynic acid (ETA) by the concurrent administration of aminoglycoside antibiotics such as kanamycin (KA). This combination can produce a sudden onset of profound and irreversible deafness[1-3] in patients given the two drugs within a short time span. No satisfactory mechanism has been proposed to account for this potent synergy that has such important clinical implications.

Glutathione (γ-glutamylcysteinylglycine; GSH) is a ubiquitous tripeptide that is known to function directly or indirectly in many important biologic functions. Such functions include protein and DNA synthesis, transport processes, enzyme activity, metabolism, and cell protection.[4] This last function, cellular protection, is important in tissues that generate active oxygen species. The cochlea, with its high rate of aerobic oxidation, is likely to generate many active oxygen compounds that would otherwise be toxic to the cells in this tissue. Under physiologic conditions, enzymes present in the cochlea probably detoxify active oxygen species and serve to protect the cochlea.[5] However, various ototoxic drugs may deplete GSH or may inactivate enzymes in the GSH pathway. For example, ETA has been shown to conjugate with sulfhydryl compounds such as GSH and cysteine. In fact, it has been proposed that ETA-cysteine is the active ototoxic species of ETA.[6,7]

Aminoglycoside antibiotics are known to be nephrotoxic as well as ototoxic. These drugs have been shown to deplete GSH from the kidney in association with nephrotoxicity.[8] Even more interesting is the finding that a free radical scavenger (WR 2721) protects against KA ototoxicity in experimental animals.[9] Because the above reports suggested the possible involvement of GSH in ototoxicity, we decided to investigate the effects of GSH depletion on the ototoxicity of the ETA-KA combination. The latter has been shown to cause a predictable, dose-dependent loss of outer hair cells and cochlear function in animals.[10]

MATERIALS AND METHODS

Auditory Brain Stem Response. Auditory brain stem responses (ABRs) were measured from 17 adult chinchillas weighing 400 to 600 g. They were anesthetized with intramuscular injections of ketamine hydrochloride (45 mg/kg) and acepromazine (2 mg/kg). Pure tones (3-ms duration with a 1.5-ms rise-fall time) were produced by an audio oscillator, shaped using a Coulbourn programmable timer and rise-fall modules that control both the signal duration and repetition rate. Tone bursts were delivered monaurally through a Sony MDR-50 transducer attached to a hollow ear bar. Stimuli of 2, 8, and 16 kHz were presented five times/s.

Stimulus intensities were measured in an artificial ear space using a quarter-inch Brüel & Kjaer microphone. Continuous tones were generated and the average sound pressure levels (re: 0.0002 dynes/

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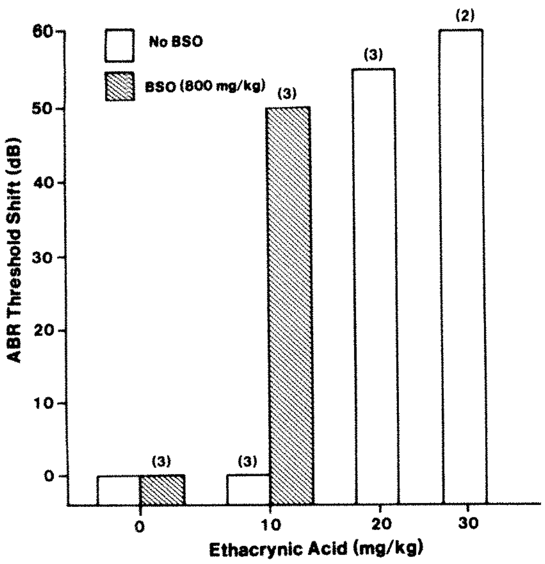

Fig 1. Dose-response relationship of various doses of ethacrynic acid (ETA) given in combination with fixed kanamycin dose (100 mg/kg subcutaneously). Positive controls represented by clear bars show auditory brain stem response (ABR) threshold shift in decibels after various doses of ETA with no buthionine sulfoximine (BSO). Experimental group (shaded bars) received BSO pretreatment to deplete intracellular glutathione. Note markedly enhanced shift of ABR threshold in experimental group. Number of animals in each group is given in parenthesis above each bar.

cm^2) recorded with a Brüel & Kjaer sound pressure level meter. Intensities were expressed in decibels attenuation from a known intensity, based on the calibration. Threshold was defined as the lowest intensity capable of producing a visually detectable, reproducible response. Thresholds were estimated using a tracking procedure in which intensity was progressively reduced until no response was observed, after which intensity was raised to confirm the intensity at which the last response was elicited.

Standard platinum alloy, subdermal needle electrodes (Grass) were used to record brain potentials differentially. The active lead was positioned at the vertex and referred to a second electrode located over the bulla ipsilateral to the stimulus. The ground electrode was located over the neck muscles. Potentials were amplified 1,000 times inside the sound-attenuating booth (bandwidth, 0.1 to 10 kHz) and viewed on an oscilloscope that further amplifies signals to produce an overall gain of approximately 70,000 times. Care was taken to ensure that the bandpass of the entire system included those frequencies that represent the ABR. The ABRs were sampled at a rate of 33,000/s (dwell time, 30 μs) for 15.4 ms following stimulus onset. Stimuli were repeated five times/s, and a total of 256 trials were averaged using a Nicolet 1170 averaging computer.

Evoked potentials were recorded prior to drug administration, 3 to 5 days and, in some cases, 30 days postadministration. The ABR measurements in control animals proved to be highly reproducible in the retest schedule, indicating a high intertest reliability.

Drug Administration. Buthionine sulfoximine (BSO) obtained from Sigma Chemical Corporation (St Louis) was given by intraperitoneal injection (800 mg/kg in phosphate buffer) after baseline ABR measurements were completed. Kanamycin sulfate (100 mg/kg) was given by subcutaneous injection at the same time. Ethacrynic acid sodium salt (Merck Sharp & Dohme) was dissolved in saline and given over the dosage range of 0 to 30 mg/kg intravenously by catheter 2 hours later.[10] Animals then were allowed to recover and were retested 3 to 5 days after the injections. The number of animals in each treatment group is given in Fig 1. Dosages of ETA and KA were selected from dose-response experiments performed in our laboratory (Fig 1), based on reports in the ototoxicity literature.[10] The combination of 10 mg/kg ETA and 100 mg/kg KA was chosen for further study, as it was shown not to have any measurable toxic action in the normal animal (Fig 1). The dose of BSO is sufficient to deplete liver GSH levels to 10% of control values within 2 to 4 hours[11] (D. W. Hoffman et al, unpublished data). Several groups of positive and negative controls were used. Normal chinchillas given no drugs formed the negative control group, chinchillas given BSO alone formed one of the positive control groups, and chinchillas given ETA in combination with KA formed another positive control group. The experimental group was given all three drugs, namely BSO, ETA, and KA.

Surface Preparations of Cochlea. Anesthetized animals were decapitated, and cochleas were perfused with fixative through the perilymphatic spaces. The primary fixative was 2% glutaraldehyde at 4°C in 0.1 *M* phosphate buffer (pH 7.2). An adequate perfusion was accomplished with a 1-mL syringe that had been fitted with the cap end of a butterfly infusion set having a short segment of tubing fitted with a micropipette. The round and oval windows were removed. In vitro perfusion was performed intermittently for 5 minutes through the round window, allowing the fluid to exit through the oval window. After perfusion and fixation, the cochleas were immersed and rotated in the same fixative for 3 hours and then placed in a refrigerator overnight.

After overnight fixation in glutaraldehyde, the cochleas were rinsed in 0.1 *M* buffer and gently perfused with the buffer through the perilymphatic spaces by loosely fitting the tube end of the perfusion syringe over the round window. Cochleas then were immersed and rotated in buffer three times for 20 minutes each time. After rinsing, the cochleas were postfixed under a fume hood by a 5-minute perfusion of 0.5% OsO_4 (at 4°C) in phosphate buffer containing 0.4% potassium dichromate. Fixation was continued by immersion and rotation (on ice) in the same fixative for 2 hours. The cochleas

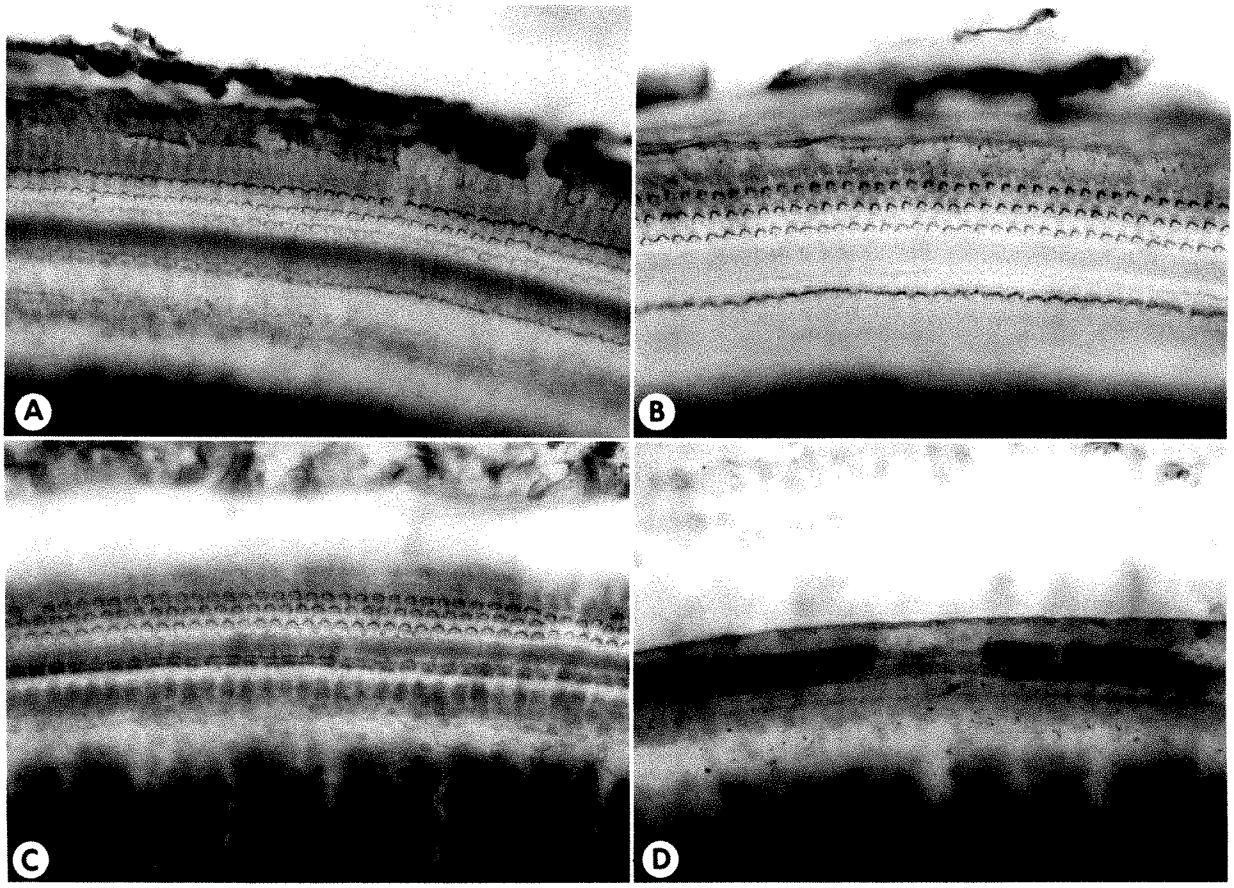

Fig 2. Photomicrographs of surface preparations from basal turns of chinchillas. A) Normal (no drug treatment). Three rows of outer hair cells with their V-shaped stereocilia can be seen, as well as single row of inner hair cells in linear array. B) Chinchilla treated with BSO (800 mg/kg intraperitoneally). C) Chinchilla treated with low dose ethacrynic acid (ETA; 10 mg/kg) and kanamycin (KA). No BSO was given. D) Chinchilla treated with BSO (800 mg/kg intraperitoneally) plus KA (100 mg/kg subcutaneously) and ETA (10 mg/kg intravenously). Total destruction of organ of Corti is present with dark shadows of membrane debris.

were rinsed in the same fashion as after glutaraldehyde fixation.

Cochleas were decalcified in the refrigerator in a solution of 0.1 *M* EDTA containing 2% glutaraldehyde. The solutions were changed daily for 2 weeks. At the end of this time, the cochleas were fully decalcified and were immersed in 2% glutaraldehyde and stored in the refrigerator.

The cochleas and the dissecting solutions were brought slowly to room temperature. The cochleas were immersed in 50% acetone in a Petri dish for 15 minutes to partially harden the tissue. Using a single-edged razor blade, the bone was trimmed away on lateral edges of the cochlea to make two flat lateral surfaces. Using a new blade, the cochlea was bisected in a midmodiolar plane along scala media landmarks with a gentle sliding motion of the blade. The cochlea was transferred into dissection solution (1 *M* $MgCl_2$ in 0.025 *M* sodium acetate buffer) for 15 minutes before staining of the cochlear tissues.

Fresh alcian blue staining solution was prepared from a stock solution of 1% alcian blue. While the cochlear halves were immersed in dissection solution, the scala media of each turn was perfused for about 30 seconds with a micropipette fitted to a syringe. The tissue was transferred to fresh dissection solution, and the scala media of each turn was rinsed with dissection solution. The cochlear halves were hardened in 50% acetone for 15 minutes for further dissecting.

The half turns from one side of the cochlea were cut by severing each turn through the modiolus and otic capsule. The half turns were labelled hook, 1A or 1B, 2A or 2B, 3A or 3B. The otic capsule was teased away from the spiral ligament, and the spiral ligament tissue from beneath the basilar membrane and the stria vascularis was removed using many small cuts with a razor blade while holding on to the tissue with forceps at the modiolus and spiral lamina region of the cochlea. Using sharp forceps, the lateral edge of the tectorial membrane was peeled away from the spiral limbus throughout the length of the half turn, and any remaining pieces of tissue (Reissner's membrane, spiral limbus, or tectorial membrane) were removed. After verifying that the basilar membrane was facing down, the half turn was transferred to a drop of Aquamount on a microscope slide and coverslipped. The slide was air-

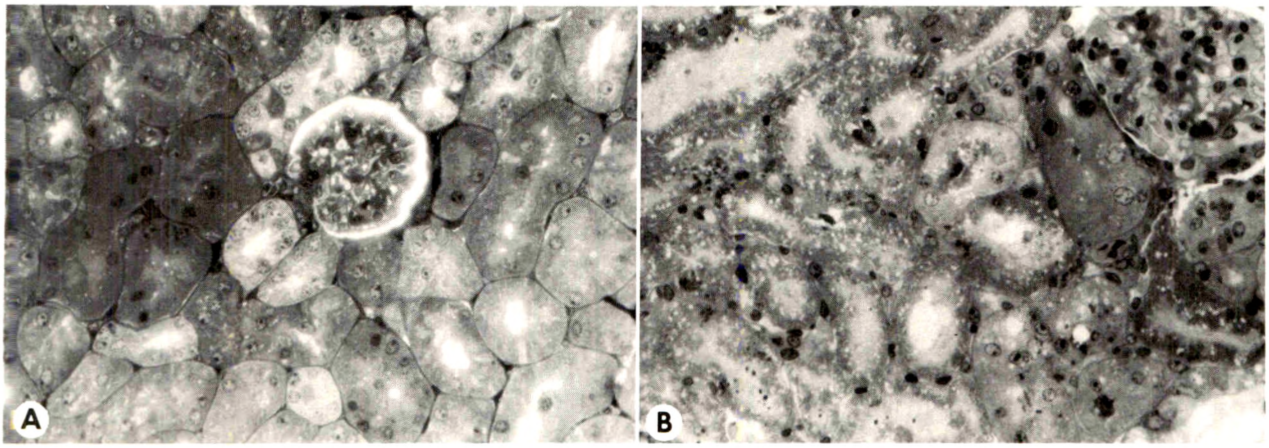

Fig 3. Light micrographs of cross sections of kidneys from chinchillas. A) Chinchilla treated with ETA (10 mg/kg intravenously) plus KA (100 mg/kg subcutaneously). No BSO was administered. Cytoarchitecture of renal tubules and glomeruli (center of field) is well preserved. B) Chinchilla treated with BSO (800 mg/kg intraperitoneally) and ETA (10 mg/kg intravenously) plus KA (100 mg/kg subcutaneously). Extensive vacuolization of tubular cells and cellular necrosis with cell debris and protein precipitates in tubular lumen are seen.

dried in a horizontal position overnight before examination under oil immersion.

Kidney Morphology. Kidneys were removed rapidly and placed in 2.5% glutaraldehyde in Millonig's buffer[12] both at 37°C. Cortical kidney regions were trimmed to 1 x 2 x 2-mm pieces. These samples were rinsed in 0.1 *M* Millonig's phosphate buffer and placed overnight at 4°C in 2.5% glutaraldehyde in Millonig's buffer. Samples were rinsed in Millonig's buffer and postfixed for 1 hour with 1.0% OsO_4 and Millonig's buffer. Following additional buffer rinses and graded ethanol dehydration, the samples were infiltrated with an ethanol-Spurr's resin mixture.[13] Samples were embedded in Spurr's resin and polymerized overnight. Using an LKB Pyramitome and glass knives, approximately 30 consecutive 2-μm sections were taken from each block. Sections were stained with toluidine blue[14] and photographed after light microscopic examination.

RESULTS

Auditory Function. The administration of ETA in doses of 20 or 30 mg/kg in combination with KA (100 mg/kg) resulted in a rapid and permanent loss of ABR in the chinchillas receiving these drugs. Animals injected with 0 or 10 mg/kg of ETA with KA were found to have no significant change in ABR threshold (Fig 1). No change in ABR threshold was detected in animals given BSO, either alone or in combination with KA only. However, a dramatic enhancement of the ABR threshold shift was observed in chinchillas receiving BSO in combination with the otherwise nonototoxic doses of ETA and KA. The addition of BSO to 10 mg/kg of ETA and 100 mg/kg KA resulted in a dramatic threshold shift in ABR. Animals treated similarly but without BSO had no significant ABR threshold change. These findings indicated a marked potentiation of ABR threshold change induced simply by the addition of BSO. This potentiation resulted in the same magnitude of ABR threshold elevation as that seen with higher doses of ETA and KA in animals not depleted of GSH (Fig 1). These findings were observed with each frequency stimulus used (2, 8, and 16 kHz), indicating widespread cochlear damage. This hypothesis was supported by the histologic findings (see below). No recovery of ABR was observed over a 30-day period of testing. Thus, the large ABR threshold elevations observed presumably were caused by extensive destruction of cochlear hair cells (see below). This resulted in a rapid and permanent shift in ABR threshold in animals receiving BSO in combination with low dose (10 mg/kg) ETA, as well as in animals receiving higher doses of ETA (20 to 30 mg/kg) in combination with KA without GSH depletion.

Cochlear Morphology. The surface preparations from normal chinchillas revealed the typical three rows of outer hair cells with V-shaped stereocilia and the inner hair cells with their stereocilia visible (Fig 2A). Animals treated with BSO alone (Fig 2B) or with low dose ETA (10 mg/ kg) combined with KA (100 mg/kg) (Fig 2C) had no significant loss of outer hair cells and could not be distinguished from controls. By contrast, the surface preparations from cochleas of animals treated with BSO followed by low dose ETA and KA revealed total loss of outer hair cells throughout the cochlea (Fig 2D). Similar morphologic findings were seen in cochleas from animals treated with high dose ETA and KA.

Kidney Morphology. Control animals (nontreated animals, animals treated with BSO, or animals treated with low dose ETA and KA) had kidneys that appeared normal by light microscopy (Fig 3A). However, chinchillas that were depleted of GSH by BSO followed by low dose ETA and KA were found to have marked vacuolization of renal tubular cells, cell necrosis, and tubular debris (Fig 3B). The only difference between the two groups of animals shown in Fig 3 was the addition of BSO to the treatment.

DISCUSSION

The data from this study strongly suggest that GSH may serve to protect the cochlea against toxicity from ETA-KA combination therapy. Chinchillas treated with 10 mg/kg ETA and 100 mg/kg KA had no significant change of ABR threshold, nor were any abnormalities of the stereocilia of the inner or outer hair cells noted on light microscopy. Ethacrynic acid is known to combine with GSH, cysteine (one of the amino acids contained in GSH), and the GSH-S-transferase enzyme.[15,16] The latter enzyme has diverse important physiologic functions, including the reduction of peroxides that may be formed during aerobic metabolism and during the metabolism of drugs.[4] The larger doses of ETA in combination with KA may overwhelm the protective effect of GSH, perhaps by interaction with this enzyme. This may result in a marked elevation of ABR threshold and loss of outer hair cells noted in animals given the larger dose combinations (20 or 30 mg/kg of ETA with KA).

Kanamycin may be metabolized in cochlear tissue to compounds that can be inactivated by GSH if the latter is present in sufficient concentration.[5] Depletion of GSH by BSO in the present study could render the cochlea vulnerable to these ototoxic substances and their metabolites, especially if the latter include free radicals.[5] Pierson and Moller[9] showed that a free radical scavenger (WR 2721) protected the guinea pig against KA ototoxicity.

The cochlear tissues contain enzymes that can detoxify active oxygen species such as hydrogen peroxide.[5] These enzymes are present in both the lateral and medial tissue compartments. In the lateral wall, the intermediate cells of the stria vascularis have been shown to contain intracellular organelles, called peroxisomes, which contain the enzyme catalase. This enzyme inactivates hydrogen peroxide, which is produced by aerobic metabolism. These same organelles also are contained in the proximal tubular cells of the kidney.[17] The combined administration of loop diuretics and aminoglycosides resulted in enhanced nephrotoxicity in the present study as well as in previous animal investigations.[18] These findings support the clinical observation that loop diuretics can enhance aminoglycoside-induced renal damage.[19] These observations may help to explain why the kidney and cochlea are damaged by GSH depletion followed by the administration of the ototoxic and nephrotoxic drug combination. If GSH is depleted from the cells in these two organs by the loop diuretics, for example, the free radicals that may be generated by the aminoglycoside may then destroy cells in the cochlea and kidney. The nephrotoxic effects may be transient, because the kidney tubules can regenerate. However, damage to the cochlea may be irreversible, since these cells do not regenerate. This would result in permanent, severe sensorineural hearing loss, which has been observed in patients treated with such combinations.[1-3,20] Buthionine sulfoximine has been shown to deplete GSH from the kidney,[11] and we have shown that it also depletes GSH from the cochlea. Control GSH levels were 175 nmol per chinchilla cochlea. On the other hand, the cochleas of BSO-treated animals were found to have only 10% of the control GSH content at 4 and 16 hours after BSO administration, and the kidneys followed a similar pattern (D. W. Hoffman et al, unpublished data). This profound GSH depletion could render both organs vulnerable to toxic metabolites of either drug or both drugs. It would be interesting to determine whether GSH supplementation protects against the ototoxicity of aminoglycosides given in combination with loop diuretics.

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XXI CONGRESS OF THE INTERNATIONAL ASSOCIATION OF LOGOPEDICS AND PHONIATRICS

The XXI Congress of the International Association of Logopedics and Phoniatrics will be held Aug 6-10, 1989, in Prague. For further information, contact the Secretariat, XXI Congress of the International Association of Logopedics and Phoniatrics, Czechoslovak Medical Society J. E. Purkyne, 120 26 Prague 2, Vitezneho unora 31, Czechoslovakia; telephone 29 41 41-4, telex 121 293.

EUROPEAN RHINOLOGIC SOCIETY

The European Rhinologic Society will hold its 12th Congress with the ISIAN meeting June 19-22, 1988, in Amsterdam. On June 23-25, 1988, a course in nasal and sinus surgery will be held in Utrecht. For further information, contact Prof Dr E. H. Huizing, Dept of Otorhinolaryngology, University Hospital Utrecht, PO Box 16250, 3500 CG Utrecht, The Netherlands.

Ann Otol Rhinol Laryngol 97:1988

ULTRASTRUCTURAL CHANGES IN VESTIBULO-OCULAR NEURONS FOLLOWING VESTIBULAR NEURECTOMY IN THE CAT

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Vestibulo-ocular (VO) neurons in the superior vestibular nucleus were labeled retrogradely with horseradish peroxidase and studied quantitatively using electron microscopy to determine the morphologic correlates of vestibular compensation. Eleven VO neurons from three normal cats were compared to 26 VO neurons in four animals killed 8 weeks after vestibular neurectomy and 13 VO cells from two animals killed 1 year after vestibular neurectomy. The results demonstrated a marked reduction (74%) in the number of synaptic profiles (SPs) on the VO cell soma in both experimental groups. Synaptic vesicles in the remaining SPs on VO neurons were fewer, smaller, and rounder than vesicles in control animals. The residual SPs also were associated with more asymmetric synapses. The experimental VO neuron showed a significant decrease in soma and organelles associated with protein synthesis.

KEY WORDS — horseradish peroxidase, neurectomy, ultrastructure, vestibular compensation, vestibulo-ocular neurons.

INTRODUCTION

Recovery from a vestibular injury (vestibular compensation) has been observed clinically for over 100 years[1] and represents one of the best-known examples of CNS recovery following a peripheral sensory deficit. Although the behavioral and physiologic correlates of vestibular compensation are well documented,[2] the precise mechanism underlying this compensatory process is incompletely known.

Behaviorally, the deficits vary somewhat depending on animal species, but in mammals the primary deficits involve the vestibulo-ocular (VO) and vestibulospinal systems. The VO disturbance is manifested as nystagmus and is a prominent clinical sign used to monitor recovery. These deficits recover rapidly within the first 3 to 6 days, with adaptation reaching completion in 6 to 8 weeks.

The physiologic correlate of the post-vestibular ablation syndrome is a rapid and complete loss of neural activity in the ipsilateral vestibular nuclear complex with increased activity in the contralateral or intact vestibular nuclei.[3-5] This sudden loss of the resting activity in both central vestibular canal and otolith neurons results largely from the peripheral deafferentation and continued commissural inhibition from the intact vestibular complex. The increased activity in the contralateral side is presumed due to the removal of commissural inhibition originating from the lesioned side.[6] A pronounced asymmetry in mean resting firing rate is the neurophysiologic correlate for the initial imbalance of head and eye position and reflexes. Several weeks following the onset of the acute injury, the mean resting activities of vestibular nuclear neurons in the two sides almost reach parity, with the ipsilateral activity slightly lower than normal and the contralateral somewhat higher.[7] The explanation for these slight inequalities is not clear, but may relate to the residual neural inputs on second order vestibular neurons.

A morphologic explanation for vestibular compensation is lacking, although some evidence has been presented to support possibilities. Korte and Friedrich[8] studied ultrastructural changes of superior vestibular nucleus neurons 5 to 6 days following vestibular neurectomy in the cat. They observed a loss of terminals containing large round vesicles and an increase in terminals with pleomorphic vesicles. They suggest that these latter terminals represent evidence of synaptic plasticity responsible for the compensatory process. Schwarz et al[9] also studied acute changes in second order neurons of the medial and descending vestibular nuclei 3 to 5 days following vestibular nerve transection in the rat. They noted a loss of small terminals with spherical vesicles, but did not observe any evidence of synaptic plasticity or axonal sprouting. Both these studies, although observing changes in the two major vestibular nuclei containing most (90%) of the type I second order vestibular neurons, did not specifically study VO neurons. Electron micrographs published in their reports demonstrated small neurons with very little cytoplasm and cleft nuclei that are similar ultrastructurally to commissural neurons (J. P. Guyot et al, unpublished observations). However, their studies also included neurons that resemble the VO neurons reported in this study. Changes observed within such a short time period (3 to 6 days) following vestibular neurectomy are not likely to represent axonal sprouting because of the short sur-

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vival period. The short survival period may not even be sufficient to permit complete degeneration of some first order neuronal terminals.

An additional approach to investigating the underlying mechanisms of vestibular compensation deals with neurotransmitters responsible for the activity changes of second order neurons. Thompson et al[10] have demonstrated an increase in γ-aminobutyric acid (GABA) levels in the ipsilateral lateral vestibular nucleus (LVN) following labyrinthectomy in the squirrel monkey, while GABA activity in the contralateral LVN was decreased. These results suggest increased inhibition from cerebellar and commissural systems that affect the vestibular nuclei. This inhibition may account for the shutdown of resting activity in the ipsilateral nuclei soon after peripheral vestibular ablation. Flohr et al[11] have reviewed the many studies dealing with the effects of drugs, both in the compensated and decompensated states following vestibular ablation. Cholinergic, adrenergic, and GABA-nergic transmitter systems have been demonstrated in the vestibular nuclei correlated with vestibular compensation and decompensation. It is likely that neurotransmitters and changes in neurotransmitters play an important role in the compensatory process.

The present study was designed to provide a quantitative ultrastructural evaluation of changes in VO neurons in the superior vestibular nucleus of the cat following vestibular neurectomy. The VO neurons were labeled with horseradish peroxidase (HRP) by injecting the oculomotor nucleus. Labeled VO neurons were studied in normal (control) animals and animals killed at 8 weeks and 1 year following vestibular neurectomy. We employed quantitative stereologic techniques to describe the ultrastructure of the VO neurons and the synaptic profiles contacting their soma. Our results indicate a marked decrease in the first order neuronal terminal contacts with the cell bodies of VO neurons at 8 weeks and 1 year after vestibular neurectomy. No evidence of reinnervation of vacated somal postsynaptic densities was observed. The vesicles in remaining terminals were smaller and tended to be rounder than in the control animals. More asymmetric synapses were seen in the remaining terminals contacting VO neurons in experimental animals than in control animals. Significant changes in the size (decrease) and the organellar composition of the VO neuron were documented at 8 weeks and 1 year following neurectomy. These observations imply a change in the metabolism of the second order neuron with possible functional consequences.

MATERIALS AND METHODS

Young adult cats 6 months to 1 year old were used in this experiment. All animals, except for two animals in the control group, were born and raised in the institutional animal colony, and all animals had known weight and sex. The series included three normal (control) animals, four animals 8 weeks post–vestibular neurectomy, and four animals 1 year post–vestibular neurectomy. Because time has not permitted study of all animals killed 1 year after neurectomy, only two animals from this group have been studied quantitatively so that their data could be included with the present material. The remaining two 1-year animals are presently under study.

Several other animals were not included in this series for various reasons: anesthesia death, failure to label VO neurons successfully with HRP, and wound infection (one animal).

Control Animals. The three control animals were anesthetized with ketamine (0.50 mL) intramuscularly supplemented by veterinary Nembutal administered intravenously (30 mg/kg of body weight) and intubated orotracheally. After a midline scalp incision was made over the occiput and underlying muscles were reflected, the bone over the cerebellar vermis and part of the cerebellar hemispheres was removed, preserving the dural covering over the cerebellum. The dura and anterior cerebellar vermis were retracted from the posterior surface of the bony tentorium down to its inferior limit near the inferior colliculi. At this point, the dura was incised and the lobules of the anterior vermis dissected from the inferior colliculi, exposing the rostral portion of the fourth ventricle and posterior aspect of the sylvian aqueduct. The midline sulcus separating the myelinated fibers of the medial longitudinal fasciculus rostral to the inferior colliculi served as a landmark for the approximate location of the oculomotor nucleus. A small glass micropipette (tip diameter, 50 to 100 μm) was inserted to the right of the midline and directed rostroventrally into the oculomotor nucleus, and 2 μL of 20% HRP in saline were injected hydraulically. After withdrawal of the pipette, Gelfoam was placed over the pipette tract. The operative site was closed loosely with chromic sutures, and skin sutures tightly approximated the skin incision. Approximately 19 to 22 hours after HRP injection, the animals were killed under general anesthesia (intravenous Nembutal) via intrathoracic intracardiac perfusion.

Experimental Animals. Under similar ketamine/Nembutal anesthesia and orotracheal intubation, a right vestibular neurectomy was performed through a ventral incision placed over the submandibular gland, which was excised to expose the auditory bulla. The bony shell of the bulla and the intrabullar partition were removed to expose the round window niche and the auditory ossicles. The lateral wall of the cochlea and vestibule were removed so that the vestibular sense organs in the vestibule could be excised. A small diamond bur was used to remove the medial wall of the vestibule and expose nerves in the internal auditory canal. The cochlear wall and modiolus also were opened to trace the entire course of the cochlear and vestibular nerves. The superior and inferior divisions of the vestibular nerve were separated from the cochlear and facial nerves in a medial direction within the internal auditory canal until the meatal opening was reached. The vestibular ganglion was located, and the nerve proximal (medial) to the ganglion was transected and bipolar cautery applied to the proximal stump of the vestibular and cochlear nerves. The bony defect then was obliterated with Gelfoam and the incision closed.

Animals were maintained on fluids administered intraperitoneally until they could feed themselves — a period which lasted from 1 to 3 days. Prophylactic antibiotics (Bicillin) also were used for 1 week. The animals were kept in 60-cm (2 ft) cubic (approximate size) cages, with regular daily exercise periods in a lighted room with a hard surface. On the day before they were killed, the experimental animals were reanesthetized and the posterior fossa craniotomy procedure described for the control animals was carried out to inject HRP into the oculomotor nucleus. Approximately 19 to 24 hours after this second procedure, the animals were anesthetized and intracardiac perfusion was performed.

Perfusion Procedure. The perfusion procedure was carried out via a cannula inserted into the ascending aorta through the left ventricle after clamping the descending aorta and opening the right auricle. Ringer's solution (250 mL at 37°C), driven by gravity, was followed by 500 mL of 0.12 *M* phosphate buffer containing 1% paraformaldehyde, 3.5% glutaraldehyde, and 34 mg/L of calcium chloride at 37°C, pH 7.2 to 7.4. An additional 1,000 mL of the same fixative was introduced at 4°C using a peristaltic pump. Total exposure to the double aldehyde fixative solution was 1 hour. The brain then was removed, and a transverse thick section was made through the oculomotor complex to verify the placement of the micropipette in the oculomotor nucleus. A 2 x 2-mm block containing the superior vestibular nucleus was removed from ipsilateral and contralateral sides and placed in 3.5% glutaraldehyde in the same buffer for 3 hours at 4° C.

After the specimen was rinsed several times in 0.12 *M* phosphate/calcium buffer, vibratome sections were cut at 60 μm. The serial sections were collected in bins, washed in several changes of 0.1 *M* cacodylate buffer (pH 7.2), preincubated for 15 minutes in diaminobenzidine (DAB) 15 mg/10 mL in 0.1 *M* cacodylate buffer containing 0.1 *M* imidazole (pH 7.0) and then incubated for 30 minutes in the same solution with the addition of 0.1 mL 1% hydrogen peroxide/10 mL.[12] After reaction, the thick sections were examined under a dissecting microscope and HRP-labeled cells were dissected out of the superior vestibular nucleus. In order to maintain orientation of the cells, the shape of the cutout was trapezoidal, with the longest vertical leg pointing ventrolaterally. Polaroid photomicrographs were taken of the sections and the position of labeled cells marked on the photos to aid in identification of the same cells under the electron microscope. These sections then were placed in 0.12 *M* phosphate/calcium buffer (pH 7.2) with 8% dextrose added, osmicated in 1% osmium tetroxide in the same buffer, washed in sodium maleate buffer (pH 6.0), and stained en bloc with a 1% uranyl acetate in sodium maleate buffer, pH 6.0. The trapezoids then were dehydrated, embedded in Spurr's resin, thin sectioned using a Sorval MT2-B ultramicrotome, mounted onto single slotted (1 x 2 mm) formvar coated copper grids, stained with uranyl acetate and lead citrate, and examined in a JEOL 100-S electron microscope. The thickness of the sections was determined by the method of Peachey[13] at 600 to 900 nm.

Quantitative Morphometric Analysis. Once a labeled cell was located in the electron microscope, the periphery of the soma was examined at a magnification of approximately 40,000 for synaptic profiles (SPs). Structures containing at least five vesicular profiles and displaying typical presynaptic and/or postsynaptic membrane specializations were classified as SPs. A single electron micrograph was taken of each profile contacting the soma in that grid. Random sections at least 1 μm apart were examined in this manner throughout the neuron. Electron micrographs of replica grids (2,160 lines/mm) were used to calculate final magnification. The negatives of the SP were projected onto a back screen (final magnification, approximately 260,000) and the eccentricity (e = c/a = semimajor - semiminor/semimajor) of the synaptic vesicles calculated by measuring the major and minor axes using a Numonics 1224 digitizer interfaced to a DEC PDP 11/73 computer. A maximum of 50 vesicles per SP were measured. The area in square nanometers was calculated from these measurements (a = 3.14159 x [semiminor axis x semimajor axis]). Examiner reliability was tested by having the examiner measure the vesicles from a group of 20 coded negatives and then several days later, without the examiner's knowledge of which negatives were repeats, having them measured again. Paired *t* tests (all statistical analyses were performed using BMDP Statistical package, Software Development Inc, Bellevue, Wash) resulted in probability values ranging from 0.85 to 0.98. Since the distribution of vesicle eccentricities within each SP were skewed, the median for this measurement was used as well as the mean area to define the vesicular content of a profile.

Organellar volume fractions of the VO neurons were calculated using point-counting morphometrics for mitochondria, nucleus, nucleolus, rough endoplasmic reticulum (RE), Golgi apparatus, and polyribosomes. Electron micrographs of three sections (one posterior, one anterior, and one through

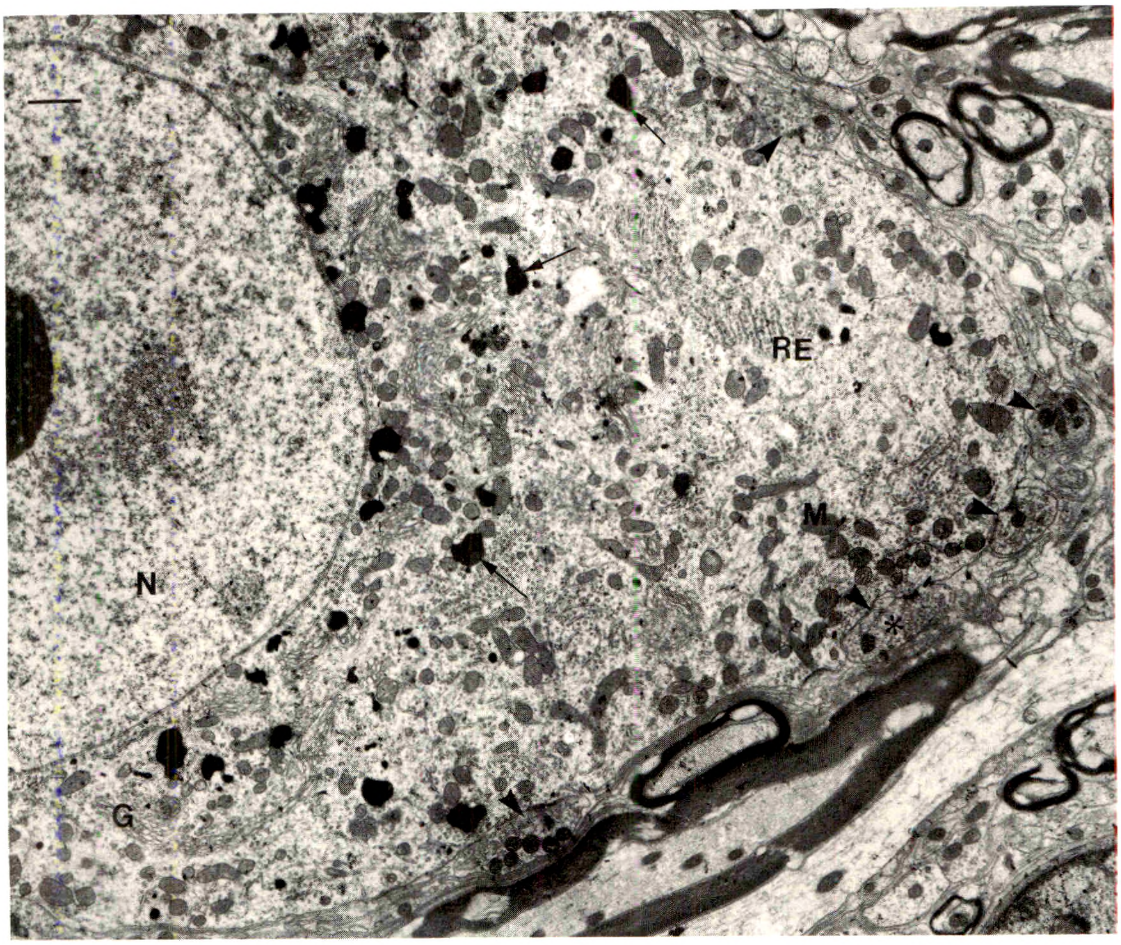

Fig 1. Control animal vestibulo-ocular neuron demonstrating prominent rough endoplasmic reticulum (RE) studded with ribosomes, abundant mitochondria (M), well-developed Golgi apparatus (G), and prominent nucleolus in large noncleft nucleus (N) (original x10,900; bar — 1 μm). A number of nerve terminals (arrowheads) contact plasmalemma membrane. Arrows — horseradish peroxidase reaction product, asterisk — see Fig 2.

the nucleolus) from each cell were taken at a magnification of 3,000 and printed, and a montage was assembled at a final magnification of approximately 8,500. A point-counting lattice (consisting of perpendicular horizontal and vertical lines placed at 1-cm increments) was placed over the montage, and wherever a linear intersection fell, the organelle beneath this point was counted. Anything that was not included in the organelles listed above was placed into a miscellaneous category of cytoplasm. The results were then calculated in percent of total counts. These data, as well as the square area of the cell at the nucleus, area of cytoplasm, area of the nucleus (which included nucleolus), eccentricity of the cell and nucleus, and average number of SPs per grid were entered into a data matrix for each cell, and analyses of variance (ANOVA) were performed within and between groups.

Unless otherwise indicated, tests for the significance of differences between groups were carried out using a one-way ANOVA[14] using a probability value of $p < .05$ as a criterion of significance.

RESULTS

Following right vestibular neurectomy, all animals showed a similar post-vestibular lesion syndrome consisting of nystagmus with the fast component directed to the left ear, falling, and head tilt to the right. In general, most animals had recovered sufficiently from these initial signs to feed themselves by the third or fourth postoperative day. One animal in the 8-week survival group recovered unusually rapidly and was able to right and feed itself at 1 day postneurectomy. The animals were set free in an open room daily for exercise and reached a level of complete compensation at 4 to 8 weeks.

Eleven cells from three control animals and 26 cells from four 8-week experimental animals were examined in this study. Data obtained from 13 cells in two 1-year experimental animals are presented for comparison of long-term changes within and around the VO neuron soma. Synaptic vesicle data, however, were not obtained in these animals. Since reconstruction of the entire dendritic tree of VO cells would have been restricted to a few cells be-

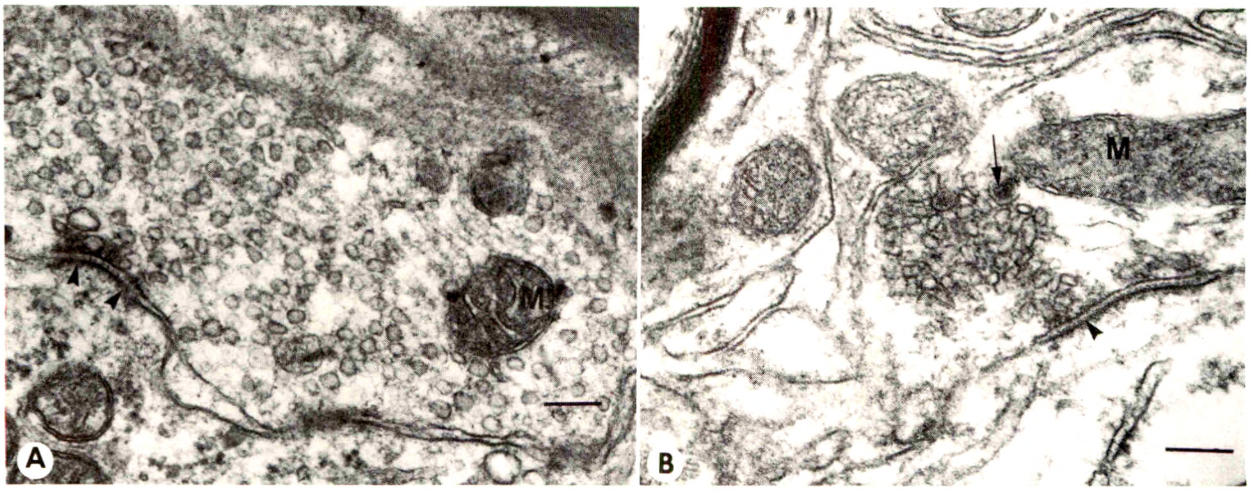

Fig 2. Boutons from control vestibulo-ocular neuron illustrating synaptic vesicles and membrane specializations. A) Terminal marked with asterisk in Fig 1 contains large round, oval, and a few flat vesicles associated with symmetric synapses (arrowheads) (original x62,300; bar — 0.2 μm). B) Another control vestibulo-ocular somal terminal filled with predominantly flattened and a few round vesicles and dense core vesicles (arrow) (original x69,000; bar — 0.2 μm). Slightly asymmetric synapse is indicated by arrowhead. M — mitochondria.

cause of time constraints, we examined several cells from a series of animals by confining our study to the cell soma. It is likely that the somal inputs are more influential in generating neural activity.[3] The VO neuronal somata in control animals are medium and large sized (20 to 40 μm) and round or oval in shape and contain a prominent noncleft nucleus surrounded by abundant cytoplasm (Fig 1). Organelles characteristic of neurons are present in significant numbers. These include mitochondria, RE, polyribosomes, Golgi apparatus, and lysozomes. Prominent SPs are scattered over the VO cell plasmalemmal membrane and contain mitochondria, synaptic vesicles, dense core vesicles, microtubules, and smooth endoplasmic reticulum (Fig 2). The vesicles in each SP range from flat to round, although some SPs appear to contain a dominant vesicle shape. Measurement of the size and shape of more

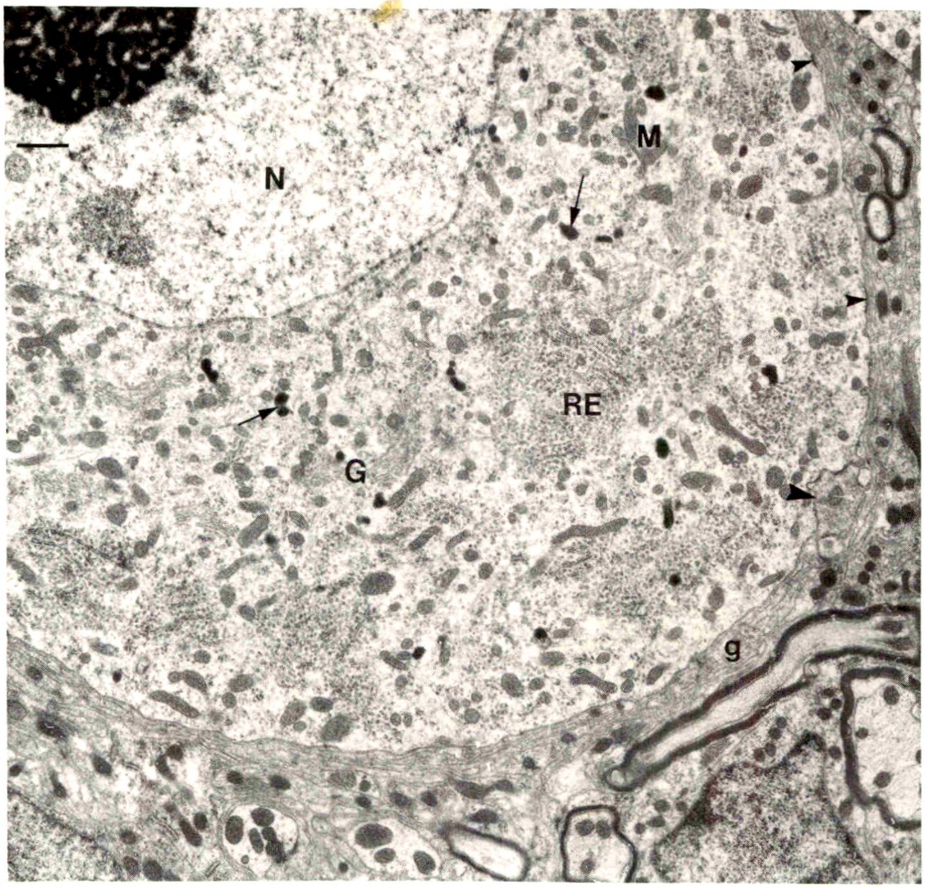

Fig 3. Experimental (8 weeks postlesion) vestibulo-ocular neuron revealing marked reduction in nerve terminals, a few vacated postsynaptic membrane thickenings (small arrowheads), and pronounced glial hyperplasia (g) (original x10,900; bar — 1 μm). Bouton (large arrowhead) is shown at higher magnification in Fig 4A. N — nucleus, M — mitochondria, G — Golgi apparatus, RE — rough endoplasmic reticulum, arrows — horseradish peroxidase reaction product.

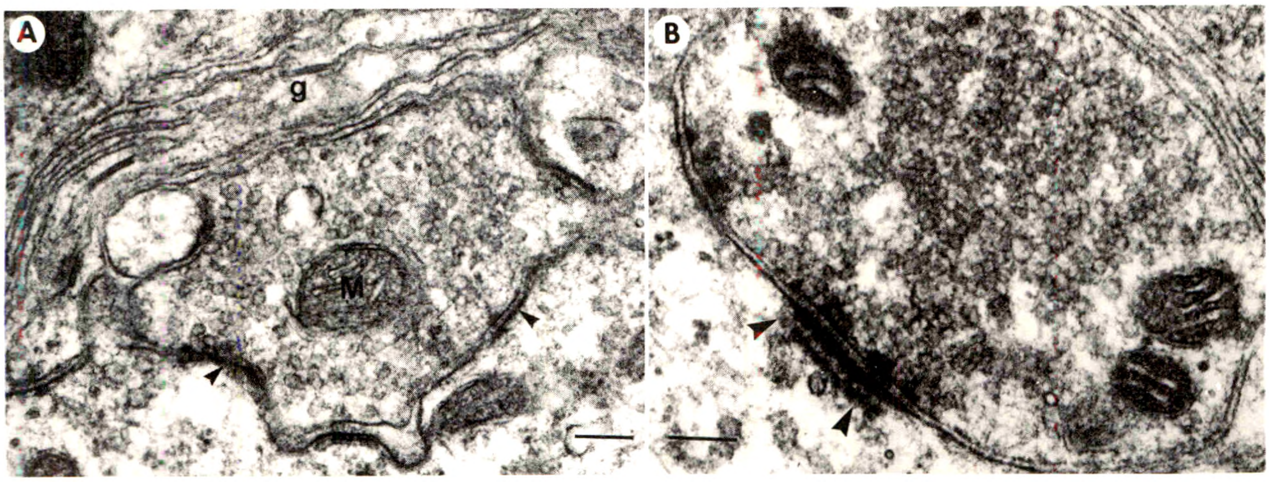

Fig 4. Boutons from 8-week experimental vestibulo-ocular neuron. A) Terminal marked in Fig 3 is filled with small round vesicles, contacting spines and forming symmetric or slightly asymmetric synapses (arrowheads) (original x62,300; bar — 0.2 μm). g — glial hyperplasia, M — mitochondria. B) Another 8-week experimental vestibulo-ocular cell terminal contains small round vesicles and very asymmetric synapse (arrowheads) (original x69,900; bar — 0.2 μm).

than 67,000 vesicles reveals a continuum rather than separate populations. Most of the synaptic membrane appositions appear symmetric or slightly asymmetric.

The most striking morphologic change 8 weeks postneurectomy is the marked decrease of SPs contacting the soma (Fig 3). The SP decreased from approximately 15 SPs/grid in the control group to four SPs/grid for the 8-week and 1-year experimental groups. Surrounding these remaining terminals and obliterating the space vacated by degenerated SP is an extensive glial cell hyperplasia. The glial cell extensions often are seen covering vacated postsynaptic membrane thickenings. Approximately 20,000 vesicles in the remaining SP were assessed. They were smaller and less flattened than those in control animals and appeared to be associated with more pronounced asymmetric synapses than in the control animals (Figs 4 and 5).

An approximate assessment was made of the presynaptic and postsynaptic densities of the SPs contacting the soma in control and 8-week experimental groups. Only electron micrographs showing clear presynaptic and postsynaptic membranes sectioned perpendicularly were used to classify the profile as asymmetric or symmetric. Examination of random fields throughout the three control animals gave a ratio of asymmetric to symmetric profiles of 0.14 (11 cells: 32 asymmetric, 226 symmetric), while a ratio of 0.4 was obtained from the 8-week postneurectomy animals (19 cells: 58 asymmetric, 145 symmetric). The asymmetric synapses associated with SPs on experimental VO neurons often displayed prominent layers of postsynaptic dense material, while the control animal VO neurons showed less dense material postsynaptically (Figs 2 and 4).

Volumetric changes were demonstrated in experimental compared to control VO neurons. The Table compares the data for the VO somal square area, organelle volume fractions, and SP somal contacts between the control, 8-week, and 1-year postneurectomy groups. There is relatively good consistency for these measurements within each group. The square area of the cell at the level of the nucleus is decreased significantly (20%) at 8 weeks and 1 year postneurectomy compared to that of control animals. The area of the nucleus, however, is simi-

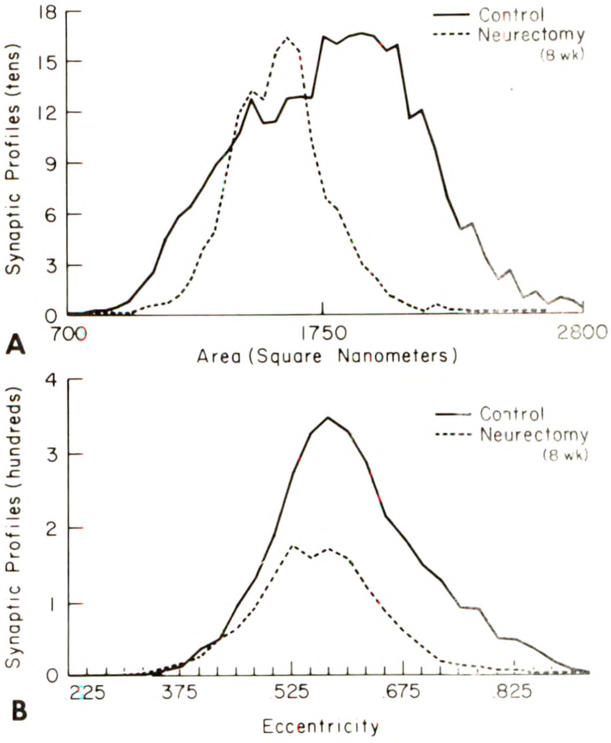

Fig 5. Graphic display of vesicle measurements from control and 8-week experimental vestibulo-ocular neurons. A) Decrease in large vesicles and increase in smaller vesicles. B) Shift to slightly rounder vesicle shape following neurectomy. There is greater decrease in flattened vesicles. Lower scale indicates round shape to left and flat to right.

MORPHOMETRIC COMPARISON OF VESTIBULO-OCULAR NEURONS

	Animals		
	Control	*8 wk Post-neurectomy*	*1 yr Post-neurectomy*
Mitochondria (%)	13.9 (±2.1)	11.9 (±2.1)	13.6 (±1.7)
Nucleus (%)	17.2 (±4.4)	20.8 (±4.9)	21.1 (±4.4)
Rough endoplasmic reticulum (%)	8.7 (±2.0)	4.2 (±1.3)	3.8 (±1.8)
Golgi apparatus (%)	4.5 (±0.9)	4.0 (±1.0)	3.9 (±0.8)
Polyribosomes (%)	34.5 (±4.4)	28.6 (±6.4)	21.4 (±2.7)
Area cell (μm^2)	729.0 (±157.0)	597.0 (±161.0)	582.9 (±142.0)
Average no. synaptic profiles/grid	15.4 (±3.4)	3.9* (±1.7)	4.4 (±3.5)
No. cells	11	26	13

Standard deviations in parentheses.

*n = 22.

lar for all groups as is soma shape (eccentricity). Point-counting data (see Table) shows that the volume fraction of mitochondria is decreased significantly (20%) at 8 weeks as are the RE (52%) and polyribosomes (17%). The decrease in Golgi apparatus at 8 weeks is not statistically significant. Preliminary data 1 year postlesion indicates that the mitochondrial volume fraction is increased to near-control levels, while the fractions of the RE and polyribosomes are even smaller than at 8 weeks postablation. The fraction of Golgi apparatus remained similar to the 8-week group. Analysis of variance showed no differences within animal groups for any of the variables measured.

A K-means cluster analysis[14] was performed using only volume fraction data to determine if there were any differences between control and experimental VO neurons, as well as between experimental groups. The analysis (Fig 6) shows a separation of control from experimental VO neurons. Furthermore, the experimental VO cells are subdivided into two clusters that reflect cells of the two experimental groups based on mean values for cell area, mitochondria, RE, polyribosomes, and Golgi apparatus. Compared to cluster B (8 weeks postneurectomy), cluster A (1 year postneurectomy) has a decrease in cell area, RE, polyribosomes, and Golgi apparatus, but an increase in mitochondria approaching control levels. This comparison suggests that VO cells from 1-year experimental animals are different from those in 8-week animals.

DISCUSSION

The experimental approach used in the present study to examine morphologic correlates of vestibular compensation was selected for several reasons. First, the superior vestibular nucleus (SVN) was

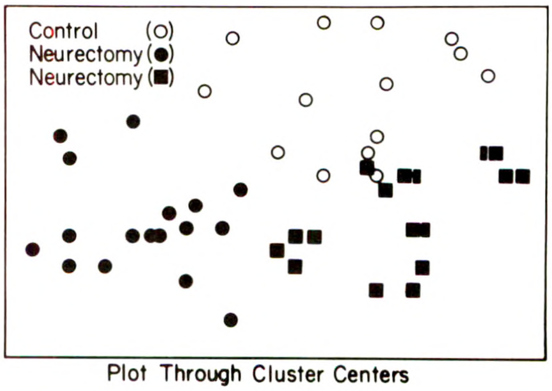

Fig 6. Graph of K-means cluster analysis of vestibulo-ocular cells based on volume fractions of soma, nucleus, and organelles, excluding data on synaptic profiles. Control and experimental neurons are separated into two groups, and there may be difference in cells within experimental groups. Coordinates are unlabeled because analysis is based on all recorded measurements describing VO cells. ● — cluster A (1 year postneurectomy), ■ — cluster B (8 weeks postneurectomy).

chosen as the source of second order VO neurons for some of the reasons outlined by Korte and Friedrich.[8] The SVN receives its peripheral input exclusively from the semicircular canal neurons.[15] Although the nucleus comprises mainly second order VO neurons, it also contains two other groups of second order vestibular neurons: commissural and vestibulocerebellar neurons.[16] The input onto these second order vestibular neurons comes from three sources: 1) the vestibular nerve, 2) the commissural neurons, and 3) the cerebellum.[16] The nucleus is well delineated anatomically and can be identified easily and accurately by light microscopy. Second, we chose to study changes concerning a single population of second order neurons, the VO neurons. Korte and Friedrich[8] and Schwarz et al[9] made no distinction regarding the identity of second order neurons studied. They described small neurons with cleft nuclei rimmed by scanty cytoplasm, as well as large and medium sized neurons with round nuclei surrounded by abundant cytoplasm. The former are similar to commissural neurons studied in our laboratory (J. P. Guyot et al; unpublished observations); the latter resemble the description of VO neurons in the present study. We found small commissural neurons to have few (four to six) terminals contacting the soma. It is probable that the morphologic changes following vestibular neurectomy may be quantitatively very different in these two classes of second order neurons. The VO neurons were identified by retrograde labeling with HRP injected into the oculomotor nucleus 20 to 24 hours prior to killing. Although other brain stem neurons whose axons project in the nearby medial longitudinal fasciculus may be labeled with this technique, we are confident of the VO neurons selected for this study. Labeled cells were harvested only from within the boundaries of the SVN. The necessity to label VO neurons in this way carried the risk that the HRP histochemistry may have an effect on the ultrastructure; however, the fixation schedules and staining procedures were maintained as closely as possible to those employed by Korte and Friedrich.[8] Since it has been shown that the synaptic vesicles remain osmotically active until osmication,[17] it is likely that our results for vesicle shape are similar.

The 8-week and 1-year survival periods following vestibular neurectomy were employed instead of the shorter survival period employed by others[8,9] for several reasons:

1. Complete degeneration of the first order vestibular neuron terminals may require longer than 1 week.
2. Neural sprouting, if it occurs, may appear and continue more than 1 week following neurectomy.
3. Functional compensation to the vestibular defect, although largely achieved at the end of 1 week, is complete at 8 weeks after ablation.

Preliminary results from animals sacrificed at 1 year after neurectomy provided an opportunity to study the long-term effects of vestibular neurectomy on second order VO neurons. Sprouting, if delayed beyond 8 weeks, may be present at 1 year. The 1-year period was also useful in studying any lasting transneuronal effects on the VO neuron of peripheral deafferentation.

The most obvious morphologic change in VO neurons occurring after vestibular neurectomy is the marked decrease in SPs making contact on the VO neuron soma. At the 8-week survival time, this loss of SPs is accompanied by a prominent glial cell hyperplasia. Perhaps glial processes present a barrier to reestablishment of neural contacts with the postsynaptic sites on the VO cell soma vacated by degenerated vestibular nerve terminals. Korte and Friedrich[8] noted a marked reduction in terminals that contained large round vesicles at 5 to 6 days after neurectomy, as well as an increase in terminals characterized by pleomorphic vesicles making contact with the cell soma. Schwarz et al[9] found in the medial and descending vestibular nuclei of the rat that small terminals containing spherical vesicles were degenerated 3 to 5 days after vestibular nerve transection. Observations in the present study support the degeneration of first order neuron terminals contacting the cell soma 8 weeks after vestibular neurectomy. The marked reduction (74%) in terminals was unchanged in the VO neurons of animals examined 1 year after neurectomy. These observations indicate that most of the input to the VO soma is provided by the vestibular nerve. The loss of this major input is largely responsible for the initial loss of neural activity in the VO neurons after vestibular neurectomy.[18]

The small number of SPs on the VO neurons at 8 weeks and 1 year postneurectomy support the conclusion that axonal or preterminal sprouting does not occur following neurectomy, at least not to the point that vacant somal synaptic sites are reinnervated. The remaining SPs on the VO neurons represent input from other afferent systems, such as commissural and cerebellar neurons. Although both of these systems exert an inhibitory action during the acute phase after peripheral deafferentation,[3-6] there is evidence that the commissural pathway assumes an excitatory role after 3 to 5 days and may be responsible for the recovery of spontaneous neural activity and increased amplitude of evoked excitatory postsynaptic potentials.[19] This return of vestibular nuclear neural activity ipsilateral to peripheral ablation corrects the asymmetry responsible for the vestibular ablation syndrome.

We assessed the vesicle population as a continuum from round to flat in shape (eccentricity) and from small to large in size. Measurements of vesicle size and shape obtained in control and 8-week animals indicate that vesicles within the residual SPs on VO neurons in experimental animals are smaller and tend to be rounder (less flattened) than in control animals (Fig 5). It is probable that most of the smaller vesicles represent a subpopulation of the control vesicle data obtained in SPs not affected by neurectomy; however, additional small round vesicles are seen postablation. These results agree in general with Korte and Friedrich's[8] observation that terminals with large round vesicles representing vestibular nerve afferents degenerated following vestibular neurectomy. Our data also demonstrate a decrease in discoid vesicles within the remaining SPs, while Korte and Friedrich[8] showed a decrease in SPs with small round vesicles and an increase in SPs containing pleomorphic vesicles. Since they studied changes 5 to 6 days after neurectomy, it is possible that their boutons with pleomorphic vesicles may represent residual terminals with vesicles undergoing a change from flat to smaller round vesicles.[20] This transition could signify a functional change in the residual SPs from an inhibitory to an excitatory mode.

Since no evidence of neural sprouting was observed at 8 weeks or even at 1 year after vestibular neurectomy, morphologic changes in remaining SPs may be indicative of mechanisms that are responsible for reactivation of VO neurons. The possible transition to smaller and rounder vesicles is one indication. Another is suggested by the qualitative assessment of synaptic membrane densities in the control versus the 8-week postneurectomy animals. More asymmetric synapses with particularly prominent postsynaptic densities associated with small round vesicles were observed in the SPs on VO neurons of 8-week postneurectomy animals compared to those in control animals. Asymmetric synapses and round presynaptic vesicles generally are associated with excitatory input.[21] This increase in the number of strong asymmetric synapses in the remaining SPs suggests a transition to a more excitatory mode of the neural input on the deafferented VO neuronal soma. Such excitatory change in commissural input has been described 3 to 5 days after labyrinthectomy in the frog by Dieringer and Precht.[19] Dynamic changes in the postsynaptic membrane of synapses may be brought about by the protein-synthesizing mechanisms of the postsynaptic cell. The amount of postsynaptic dense material has been shown to change with alterations in activity of the system or neurotransmitter. In the visual[22,23] and auditory systems,[24] deprivation of stimulation transforms symmetric synapses into asymmetric by increasing the postsynaptic membrane densities. Prolonged administration of GABA (3 to 7 days) induces postsynaptic densities in neurons of the superior cervical ganglion of the rat.[25] In this loose context, it is possible that decreased stimulation (deafferentation) of vestibular system activity may play a role in converting synaptic specializations of residual inputs to the VO neurons. The increased GABA levels in ipsilateral vestibular nuclei produced in response to peripheral ablation[10] also may be instrumental in the conversion to more asymmetric synaptic membrane specialization on VO somata.

Point-counting data from the VO neuron soma revealed a significant volumetric decrease in cell size, RE, and polyribosomes, while the size of nucleus (and nucleolus) remained constant. The Golgi apparatus in VO neurons showed a slight decrease at 8 weeks and 1 year. The implication of these decreases in VO neuron organelles is that there is a change in the VO neuron's capacity for protein synthesis, maintaining structure, and responding to increased demands upon its activity. Although rapid turnover and replenishment of proteins (neurotransmitter) occurs at the termination of VO neurons on oculomotor neurons, the reservoir responsible for maintaining sufficient baseline levels of neurotransmitter probably is located within the soma. It is possible that the postablation VO neuron may not be able to keep up with unusual demands upon this source of transmitter material. These transneuronal changes in the VO neuron probably are dependent on the decrease in the area of postsynaptic membrane contacted by active afferent input to the cell.

SUMMARY

In this study we attempted to describe morphologic correlates to the behavioral and neurophysiologic events of compensation following peripheral vestibular ablation. Quantitative ultrastructural techniques were used on VO neuron somata in the SVN of normal and 8-week and 1-year postneurectomy cats. At these survival periods when compensation was complete, the 74% reduction in terminals contacting the soma represents the loss of excitatory vestibular nerve input and indicates that neural sprouting to reinnervate the vacant somal synaptic sites is not a mechanism responsible for return of neural activity in the SVN. Changes in the remaining boutons (commissural or cerebellar) on the VO somata suggest a reactive synaptogenesis providing a more excitatory mode. These are 1) a change to smaller and rounder (less flattened) vesicles and 2) formation of more asymmetric synapses. Such an excitatory change in the commissural system has been proposed as responsible for the restoration of spontaneous and evoked nuclear activity following peripheral ablation. The VO neuron shows a 20% reduction in cell volume when deprived of vestibular nerve input for 8 weeks or longer. Moreover, there is a significant decrease in RE (52%) and ribosomes (17%), organelles responsible for protein synthesis. These transneuronal changes in the VO neuron may have functional implications.

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NINCDS NOTES*

COCHLEAR IMPLANTS CONSENSUS CONFERENCE

The National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) announces a consensus conference on cochlear implants to be held May 2-4, 1988, in the Masur Auditorium of the National Institutes of Health (NIH) Clinical Center in Bethesda, Maryland. The purpose of the conference is to reach agreement on important issues in cochlear implantation. The key questions to be addressed are: 1) Who is a suitable candidate for a cochlear implant? 2) What are the advantages and disadvantages of the different types of cochlear implants? 3) How effective are cochlear implants? 4) What are the risks and limitations of cochlear implantation?

Since the development of cochlear implants in the 1960s, more than 1,000 patients — children and adults — have received one of a variety of these devices. Controversy exists on several issues, such as whether to select single electrode or multielectrode devices, and how to choose suitable preimplantation and postimplantation assessments and rehabilitation procedures. Specialists in otolaryngology, auditory anatomy and physiology, rehabilitative audiology, speech and language disorders, and other relevant fields will be among conference speakers who will present current scientific thinking with regard to the issues. Representatives from concerned voluntary organizations will make statements as well, and ample time will be provided for participants to interact and to voice contrasting views. On the final day of the conference, the consensus panel will present a draft report and invite comments from the audience. The panel then will amend the consensus statement as called for and will prepare a final draft for distribution to the interested biomedical and public communities.

The conference is sponsored by NINCDS, the NIH Office of Medical Applications of Research, the National Institute on Aging, the National Institute of Child Health and Human Development, the Veterans Administration, and the Food and Drug Administration. To obtain further information or to register for the cochlear implants consensus conference, contact Nancy Cowan, Prospect Associates, Suite 500, 1801 Rockville Pike, Rockville, MD 20852.

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NEURONS OF THE INFERIOR MEDULLARY VELUM IN THE CEREBELLOPONTINE ANGLE

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LOS ANGELES, CALIFORNIA

The edge of the inferior medullary velum (tenia) is attached in part to the surface of several structures localized in the cerebellopontine angle, including the cochlear nuclear complex and the pontobulbar body. Since superficial layers of these structures contain numerous neurons, we examined the possibility that neurons are also present within the velum. On light microscopy, we found groups of neurons accumulated immediately under the pia mater covering the tenia. The number of groups in different specimens varied from one to three, and the groups were rounded or oval in shape. A bundle of fibers running from the main mass of the brain stem toward these groups was revealed with a myelin-staining technique. The majority of neurons in the groups were angular in shape. These findings may contribute to our understanding of the general and surgical anatomy of the cerebellopontine angle.

KEY WORDS — cochlear nuclei, medullary velum, neurons, pontobulbar body.

It has been demonstrated recently that the inferior velum of the fourth ventricle is attached to the surface of the cochlear nuclear complex (CN).[1] The velum separates the larger, intraventricular portion of the CN located within the lateral recess of the ventricle from its smaller, extraventricular portion and also from the root of the vestibulocochlear nerve. A part of the velum, the tenia, may serve as a landmark in surgery of the cerebellopontine angle. It also has been suggested that making an incision in the tenia could be helpful for placement of the central electroauditory prosthesis for stimulation of the CN.[1] Therefore, we felt it was important to examine the histologic features of this structure.

In addition to the CN, the tenia is attached to the cerebellum and other structures located in the angle, including the pontobulbar body (PBB), which is adjacent to the ventral and caudal boundaries of the CN.[2] Since the tenia is in direct contact with the CN and the PBB, the outer layers of which contain numerous neuronal populations, we assumed it might contain some neurons as well. Relatively extensive developmental processes in the area, including the complex process of cell migration from the lateral lip of the rhomboid fossa toward the ventral surface of the brain stem,[3] and also some structural variations in this area in adults[4] were additional reasons to suspect the presence of neurons in the tenia. The purpose of this study was to confirm their presence and to describe their characteristics.

MATERIALS AND METHODS

The tissue blocks containing the CN, PBB, caudal

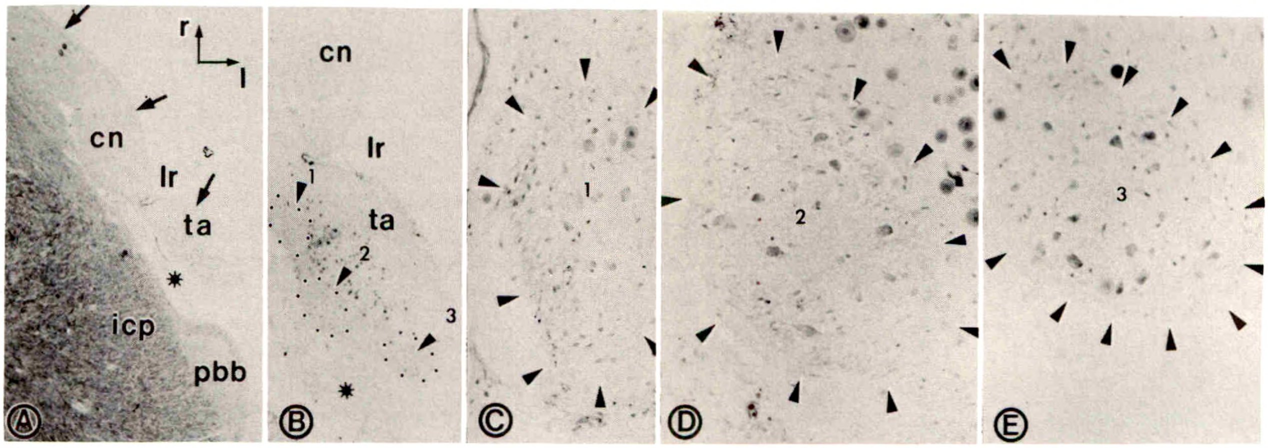

Fig 1. Right side of brain stem (paraffin; cresyl violet–Luxol blue). A) Photomicrograph of horizontal section through tenia (ta), cochlear nuclei (cn), pontobulbar body (pbb), and inferior cerebellar peduncle (icp) (original x9.5). l — lateral, r — rostral, lr — lateral recess, arrows — ependyma within lateral recess of fourth ventricle, asterisk — pia mater and subarachnoid. B) Adjacent section, in which three groups of neurons (dots and arrowheads) are numbered (original x30). C) Group of neurons (No. 1 in B) located closest to brain stem (original x150). D) More remote group of neurons (No. 2 in B) (original x150). E) Group of neurons (No. 3 in B) most remote from brain stem (original x150).

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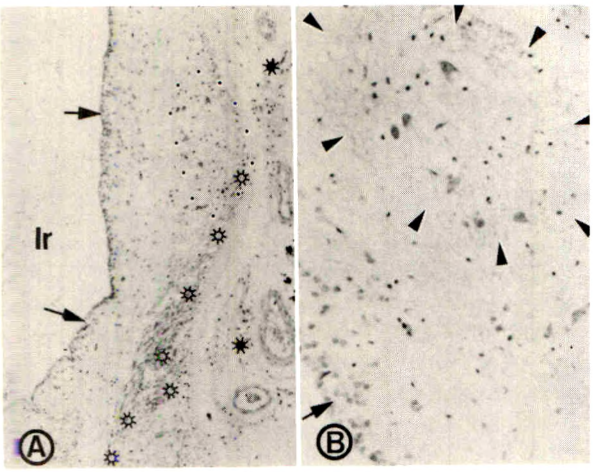


Fig 2. Horizontal sections through another specimen showing A) bundle of myelin-containing fibers (empty asterisks) running between brain stem and neurons in tenia (paraffin; cresyl violet–Luxol blue; original x45). B) Same group of neurons at higher power (original x110). Other markers as in Fig 1.

portion of the cerebellum, and a part of the tenia were dissected out from eight postmortem adult human brains fixed in 4% buffered solution of formaldehyde. They either were frozen with liquid nitrogen or dry ice or were embedded into paraffin or celloidin. The sectioning plane (horizontal) was parallel to the caudorostral axis of the brain stem. Serial sections were cut and then stained with cresyl violet–Luxol blue according to the technique of Klüver and Barrera[5] or with hematoxylin and eosin.

RESULTS

Figure 1 shows the appearance of the right side of the brain stem in the area of the cerebellopontine angle in its dorsal part. The part is dorsal to the roots of the vestibulocochlear and facial nerves. Since the flocculus was removed, the cerebellum is not seen; only a medullary part of the angle (inferior cerebellar peduncle, PBB, CN, etc) is seen in this picture. In Fig 1A, a relatively small part of the tenia is seen as being attached to the CN. The PBB is caudal to the tenia. The ependyma covers the intraventricular side of the latter, while the extraventricular side is covered by the pia mater and the subarachnoid.

An adjacent section from the same region is shown in Fig 1B. In all specimens studied, neurons were found in the tenia. In this particular brain stem, the neurons appeared to be accumulated in three groups rather than scattered through the whole strip of the tenia. The groups are located in the vicinity of the caudal part of the CN and the anterior boundary of the PBB. In this specimen, they are in the vicinity of the brain stem surface and are located immediately under the extraventricular surface of the tenia, ie, under the pia mater covering the velum. The groups are round or oval in shape. The shorter axis of the groups is oriented perpendicular to the surface of the tenia. These groups of neurons are shown at higher magnification in Fig 1C-E. The groups are seen well in preparations stained with H & E or cresyl violet–Luxol blue and are distinguished in the tissue of the tenia not only because of their neuropil, but also because of their fiber content. In the majority of specimens, the fibers run in different directions within the individual groups and they also form a layer around the groups.

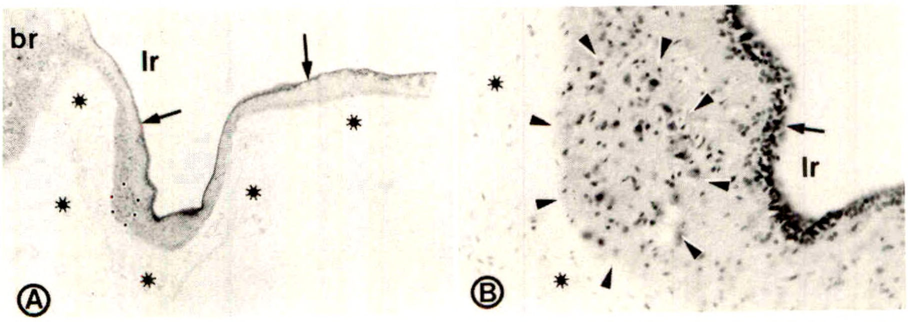
A bundle of myelinated fibers running from the main mass toward the neuronal groups in the tenia was observed in preparations stained with Luxol blue (Fig 2A). We were not able to determine the specific area of origin of the bundle or of its termination in the brain stem because of the extensive saturation of the area with other fiber tracts (for example, the inferior cerebellar peduncle). Figure 3 demonstrates the appearance of one group of neurons in the tenia. The group is more remote from the surface of the brain stem than in the previous sample. In general, the distance varies significantly in the brain stems examined. The number of the groups also varies from one to three. However, the presence of only one group is characteristic of the majority of the specimens.

Figure 4 demonstrates a number of cell types characteristic of the tenia. In general, neurons that are angular in shape are the most numerous. However, there are also neurons with oval contours (Fig 4C). The neurons differ in size as well. They could be described as small, pyramidal, oval, large, elongated, and multipolar. There was no specific topographic distribution of the neurons within the groups.

DISCUSSION

We have described the morphologic and topo-

Fig 3. Photomicrographs of horizontal section from another brain showing tenia (celloidin; H & E). A) Group of neurons (dots) located at significant distance from main mass of brain stem (br) (original x15). B) Same group of neurons (arrowheads) at higher power (original x90). Other markers as in Fig 1.



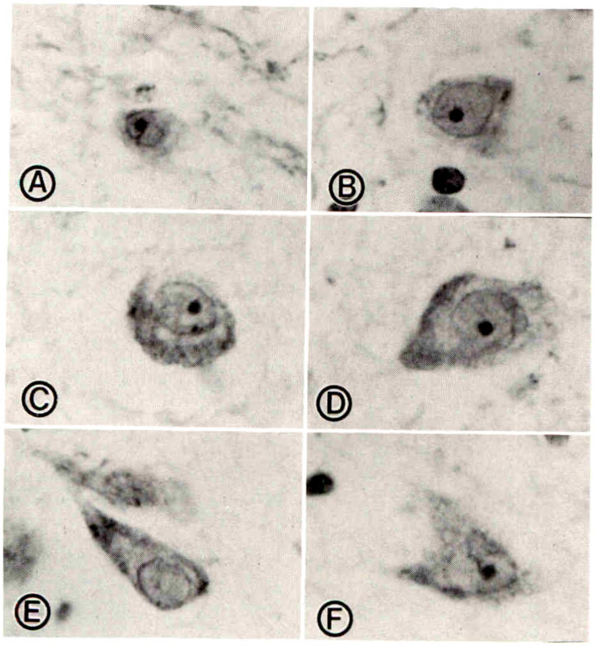


Fig 4. Photomicrographs of neurons characteristic of tenia in cerebellopontine angle (cresyl violet–Luxol blue; original x860). Neurons are A) small, B) pyramidal, C) oval, D) large, E) elongated, and F) multipolar.

graphic characteristics of the neurons in the tenia of the inferior velum. Because the accumulations or groups were present in all the specimens studied, they seem to be a typical structure of the human brain rather than a variation. At the same time, variations in the local topographic specificities of the groups, including the distance from the main mass of the brain stem, seem to be obvious. The size of the groups is perhaps another parameter that might vary. We did not conduct a quantitative study of this variability. Details of the connections between the neurons in the tenia and the brain stem remain unclear. Although there are fibers running between the nucleus and main mass of the brain stem, it would be difficult without special techniques or certain histopathologic changes to conclude where in the brain stem they originate or terminate. We only may speculate that at least a fraction of them could reach the CN because the attachment of the tenia to the CN was observed in a number of specimens examined in the present work. However, we also have observed that the tenia is attached to the PBB and the area localized between them.

The neuronal content of the tenia is not completely similar to that of the CN or the PBB. Indeed, it is known that the caudal ventral CN is characterized by the presence of the globular type of neurons. Only a few occasional oval-shaped neurons that bore certain similarity to the globular neurons were seen in the tenia. The PBB is characterized by significant variations in the neuronal types populating it.[6] Many of them are angular in shape, and in this respect they might be similar to the tenial neurons. The dorsal CN also contains a number of neuronal types that are angular in shape (multipolar, pyramidal, etc). These similarities, however, may be superficial and without relation to the origin of the neurons found in the tenia.

The functional role of the neurons in the tenia is not clear. However, they might be important because of their suspected connections with the neighboring CN. If they are related to the PBB, their functional significance would be difficult to determine without appropriate experimental conditions. It has been shown that the PBB could be related to the auditory- and visual-related areas in the cerebellum as well as to the red nucleus and spinal cord.[7]

The data obtained in the present investigation may be useful for the better understanding of the general and surgical anatomy of the cerebellopontine angle, which is a relatively frequent object of surgery. The surface of the CN also is used for implantation of the electroauditory prosthesis.[8,9] Since the prosthesis is placed partly within the lateral recess, the inferior velum, including its tenia, could be among structures of the angle involved in this procedure. This study confirmed the presence of neurons in the tenia and described some of their anatomic characteristics.

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HEARING PRESERVATION IN UNILATERAL ACOUSTIC NEUROMA SURGERY

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This paper reviews the principal English literature on hearing preservation in unilateral acoustic neuroma surgery. Seventeen case reports and 13 surgical series are included. In addition, we report ten cases of our own, two with successful hearing preservation. The purpose of this report is to study feasibility, success rate, and associated problems. Previous reports have been compared in terms of criteria that we have selected. A classification system similar to Silverstein's is used. The total number of cases under review is 621, with 221 reported successes. Cases limited to those having a unilateral acoustic neuroma, with valid supportive audiometry, were 394, with 131 successes. The approximate overall rate of success is 33%. There are five cases of hearing preservation with unilateral acoustic neuromas 3 cm or larger when supporting audiometric data are available, the largest being "4-5 centimeters." Problems included mixing of unilateral acoustic neuromas with other types of tumors and failure to include comprehensive data, particularly audiometry. We conclude 1) that hearing preservation is a reasonable goal in unilateral acoustic neuroma surgery, although the number of available candidates is relatively small and 2) that intelligent selection of patients and high quality surgical technique are the keys to success.

KEY WORDS — acoustic neuroma, cerebellopontine angle tumor, hearing preservation, middle fossa approach, suboccipital approach.

INTRODUCTION

Rapid progress in the surgical management of acoustic tumors has taken place over the past quarter century. One of the more controversial elements of this progress has been the effort to preserve hearing in selected cases. This paper reports the results of a survey of the literature pertinent to this subject to determine the feasibility, success rate, and problems involved. We also report our own experience in the surgical treatment of ten patients with unilateral acoustic neuromas.

REVIEW

In order to answer these questions, and perhaps to identify others, we carried out a survey of the literature relating to this subject. We limited this review to the subject of attempted hearing preservation (HP) in the surgical treatment of unilateral acoustic neuromas as reported in the English language medical literature. Initially, we further limited our search to comprehensive reports of surgical series as opposed to case reports. Because of the tendency of authors writing on this subject to produce multiple serial reports, we used a Medline search beginning in 1980 in an attempt to identify the most current reports available.

The process just described also identified a number of articles on this subject that best can be described as case reports, published as early as 1954. For their historical interest, and also in an effort to clarify a certain amount of folklore on this subject, we decided to review these reports as well.

In order to compare the various reports included in this study in a meaningful and useful way, it has been necessary to develop criteria for each group of reports. These criteria have not always coincided with the criteria used by the original authors, and it has been necessary in some instances to reorganize or even recalculate some of their data. The possibility therefore exists that we may have misinterpreted these data, or made errors in extrapolating them. Considerable effort has been made to avoid such errors. In analyzing the earlier papers, we have sometimes applied current standards to older data, such as with facial nerve evaluation; and in some instances this may be unreasonable.

The essence of this portion of our study is contained in Tables 1 and 2. Annotations within the Tables are explained in the accompanying codes.

Case Reports. The 17 reports[1-17] included in this aspect of our study are identified in Table 1 by the primary authors involved, and data pertinent to each study are displayed in the vertical columns beneath each primary author's name. Note that HP was reported as early as 1954 by Elliott and McKissock.[1] Line 2 displays the number of cases of HP claimed by the authors, and totals 36 cases among the 17 reports.

Fourteen of the 17 reports described exclusive use of the suboccipital rather than the middle fossa approach. Line 4 indicates whether or not a clear description of the method of opening the internal auditory canal (IAC) during suboccipital surgery was provided, which would imply, according to current standards, that complete removal of that portion of the tumor was likely to have been accomplished. Only nine of 15 suboccipital reports included such a description.

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Presented at the meeting of the American Otological Society, Inc, Denver, April 26-27, 1987.

REPRINTS — Gale Gardner, MD, 899 Madison Ave, Suite 602A, Memphis, TN 38103.

TABLE 1. LITERATURE SURVEY OF CASE REPORTS

	PRIMARY AUTHOR	McKissock	MacCarty	Malis	Rhoton	Bucheit	Yasargil	Sugita
1	Year of Study	1954[1]	1975[2]	1975[3]	1976[4]	1977[5]	1977[6]	1979[7]
2	No. of Cases with Hearing Preservation Reported	3	3	8	1	?	1	3
3	Surgical Approach (SO=suboccipital, MF=middle fossa)	SO	SO	SO	SO	SO	SO	SO
4	Internal Auditory Canal (IAC) Exposure Described	No	No	Yes	Yes	Yes[B]	Yes	No
5	VIIIth Nerve Monitored	No	No	No	No	No	No	Yes[D]
6	Tumor Size Reported	1, 1.5, 1 cm	No	No	1 cm	No	2 cm	3.5, 4, 4.5 cm
7	Total vs Subtotal Removal Reported	Yes	Yes	No	Yes	No, but implied	No	Yes
8	Comprehensive Report of Complications	Yes	Yes	No	No	No	Yes	Yes
9	Comprehensive Report of Facial Nerve Results	Yes	No	No	Yes	No	No	No
10	Valid Pre- and Post-operative Audiometry	No	No	No	No	No	No	No
11	Success Rate (Based on Authors' Criteria)	3/3	3/15	8/12	1/?	"2/3rds"	1/?	3/22
12	Patients' Subjective Success Rate	No	No	No	No	No	No	No
13	One-year Follow-up Data Reported	No	No	No	No	No	No	No
14	Significant Improvement in Hearing with Valid Audiometry	No (Claimed one)	No	No[I]	No	No	No	No (Implied)
15	Hearing Preservation in 3 cm or Larger Tumors with Valid Audiometry	No	No	No	No	No	No	No[L]
16	Success Rate (Gardner Criteria)	NA	NA	NA	NA	NA	NA	NA
17	Relationship of Hearing Preservation to Tumor Size	No	No	No	No	Yes[M]	No	No
18	Relationship of Hearing Preservation to Degree of Hearing Loss	No	No	No	No	Yes[N]	No	No
19	Criteria Reported on Measurement of Tumor Size by CT	No	No	No	No	No	No	No
20	Criteria Reported on Measurement of Tumor Size at Surgery	No	No	No	No	No	No	No
21	Mortality Reported for Hearing Preservation Cases	Yes (0)	No[O]	Yes (0)	Yes (0)	Yes (0)	Yes (0)	Yes[P] (1)

CODE FOR TABLE 1

A. In one case, used MF and SO.
B. Stated it *may* be necessary.
C. Stated porus was opened, but provided no details.
D. Direct eighth nerve monitoring (apparently first such use).
E. ABR.
F. Preoperative and postoperative audiometry, but no speech discrimination test given, and no details of whether adequate masking was used.
G. Apparently valid audiometry, except no details of masking provided.
H. Audiometry without masking details in one case; no audiometry in second case.
I. Quote by Ojemann in Fischer et al[9] that audiometry showed improvement in three of 24 patients.
J. Masking not mentioned.
K. Masking not mentioned, and no speech discrimination reported.
L. Author stated that audiometry showed HP in three cases, having tumor sizes of 3.5, 4.0, and 4.5 cm.
M. Tumor must be smaller than 2 cm.
N. Patient must have some residual hearing preoperatively.
O. Mortality results not correlated with HP series.
P. Death occurred 16 months postoperatively, with infarction of pons and residual tumor present.

In only five of 17 reports was the use of surgical monitoring of cochlear nerve function described. Four of these were by auditory brain stem response (ABR), of which one[7] in 1979 claimed the first use of direct monitoring of the eighth cranial nerve.

The tumor size was reported for 16 of the 36 cases in which HP was claimed. One author reported HP in a 5 x 7-cm tumor. A clear statement was made in 12 of the 17 reports as to whether total or subtotal tumor removal had been accomplished. A complete report of complications was provided in ten reports, and a comprehensive report of facial nerve outcome was provided in four of 17 reports. Valid audiometric findings, including the apparent use of masking and speech discrimination, were given in only four

Bremond	Fischer	Tarlov	Chai	Wigand	Hardy	Rand	Haines	Mikaelian	Wiet	TOTALS
1980[8]	1980[9]	1980[10]	1981[11]	1981[12]	1982[13]	1982[14]	1985[15]	1985[16]	1986[17]	1954-1986
4	1	1	1	1	2	2	1	1	3	36
SO[A]	SO	SO	SO	MF	SO/MF	SO	SO	SO	MF	SO=14, MF=2, SO/MF=1
Yes	No[C]	Yes	No	NA	No	Yes	Yes	Yes	NA	No=6, Yes=9
No	No	No	No	No	Yes[E]	Yes[E]	No	Yes[E]	Yes[E]	No=12, Yes=5
1.5, 2, 3, 5 cm	3 cm	No	5x7 cm	Yes?	2 cm, ?	No	1 cm	4-5 cm	No	No=6, Yes=11
Yes	Yes	Yes	Yes	Yes?	Yes	No, but implied	Yes	Yes	No	No=5, Yes=12
No	Yes	Yes	No	No	No	Yes	Yes	Yes	Yes	No=7, Yes=10
No	Yes	No	Yes	No	No	No	No	No	No	No=13, Yes=4
No[F]	Yes[G]	Yes[G]	No[F]	No	No[H]	No	Yes	Yes	No	No=13, Yes=4
4/?	1/?	1/?	1/?	1/10?	2/?	2/?	1/?	1/?	3/6	36/?
No	No	No	No	No	No	No	Yes	Yes	No	No=15, Yes=2
No	No	No	No	No	No	No	No	Yes	No	No=16, Yes=1
No	Yes[J]	No	No[K] (Claimed one)	No	No	No	No	No	No	No=16, Yes=1
No[K] (Claimed two)	Yes[J] (3 cm)	No	No[K] (Claimed one)	No	No	No	No	Yes (4-5 cm)	No	No=15, Yes=2
NA	Class 1=1[J]	Class 2=1[J]	NA	NA	Class 2=1	NA	Class 2=1	Class 1=1	NA	Class 1=2 Class 2=3
No	Yes	No	No	No	No	No	No	No	No	No=15, Yes=2
No	Yes	No	No	No	No	No	No	Yes	No	No=14, Yes=3
No	No	No	No	No	No	No	No	No	No	No=17, Yes=0
No	No	No	No	No	No	No	No	No	No	No=17, Yes=0
Yes (0)	Yes (0)	Yes (0)	Yes (0)	No[0]	Yes (0)	No[0]	Yes (0)	Yes (0)	No[0]	No mortality=12 Mortality=1 No data=4

of 17 reports.

It was not possible to determine the overall success rate claimed by all authors, because of failure in 11 of the 17 reports to provide the total number of cases in which HP was attempted. In the remaining six reports with available data, the success rate reported was 21 of 68 (31%).

In only two reports was there an indication given as to the degree of subjective success experienced by the patients, and 1-year follow-up was provided in only one of the 17 reports.

Part of the folklore of acoustic tumor surgery are the statements often made regarding HP in patients having large tumors, or significant improvement in hearing following acoustic tumor surgery. When subjected to the requirement that valid-appearing audiometric findings be reported, there were but two apparent instances of HP in patients having tumors of 3 cm or greater diameter (3 cm[9] and 4 to 5 cm[16]), and only one instance of apparent HP with actual improvement in hearing.[9]

Table 3, which will be discussed later, was developed as part of this study to provide audiometric criteria for the classification of HP into five categories. Using these criteria, an effort was made to classify the 36 patients reported in these 17 studies according to degree of surgical success. Because of lack of data or quality of data, only five patients could be classified, and for two of these it was not certain that appropriate masking had been used.

Two authors suggested a possible relationship be-

TABLE 2. LITERATURE SURVEY OF SURGICAL SERIES

	PRIMARY AUTHOR	Glasscock	Harner	Jannetta	Nedzelski	Ojemann
1	Year of Study	1982[18]	1984[19]	1984[20]	1984[21]	1984[22]
2	No. of Cases with Hearing Preservation Attempted	16(?)	61(?)	9	25	22 (34)[A]
3	Study Limited to Unilateral Acoustic Neuromas	No	No	Yes	No	Yes
4	Complete Data on All Patients in Series	No	No[B]	Yes	No[B]	Yes[C]
5	Valid Pre-op Audiometry for All Patients in Series	No	No[B]	Yes	No[B]	Yes[C]
6	Pre-op Tumor Size Reported for all Patients in Series	No	?	?	?	?
7	Criteria for Surgery Reported	Yes	Yes	Yes	Yes	Yes
8	Surgical Approach	MF SO?[G]	SO	SO	SO	SO
9	Internal Auditory Canal (IAC) Exposure Described	NA	Yes	Yes	Yes	Yes
10	VIIIth Nerve Monitored	No	No	Yes[I]	Yes[J]	Yes[J]
11	Surgical Tumor Size Reported for All Patients in Series	No	No[B]	Yes	No	Yes
12	Total vs Subtotal Removal Reported for All Patients in Series	No	No	Implied	Yes	Yes
13	Comprehensive Report of Complications	No	Yes	Implied	Yes	Implied
14	Comprehensive Report of Facial Nerve Results	No	No	No	No	No
15	Valid Post-op Audiometry for All Patients in Series	No[N]	Yes	Yes[E]	Yes	Yes[C]
16	Criteria for Success Reported	Yes	Yes	Yes	Yes	Yes
17	Use of Data Processing Indicated	No	No	No	No	No
18	One-year Follow-up Data Reported	No	No	No	No	No
19	Patients' Subjective Success Rate	No	No	No	No	No
20	Significant Improvement in Hearing with Valid Audiometry	No	Yes[O] (3)	Yes[P] (1)	Yes[Q] (1)	No[R]
21	Hearing Preservation in 3 cm and Larger Tumors with Valid Audiometry	No	Yes (4 cm)	No	No	Yes (4 cm)
22	Success Rate (Gardner Criteria)	NA	Class 2=3, 3=4 5=6	NA	Class 1=1, 2=2 3=2, 5=1	NA
23	Relationship of Hearing Preservation to Tumor Size	Yes	Yes	?	?	Yes
24	Relationship of Hearing Preservation to Degree of Hearing Loss	?	Yes	?	?	?
25	Criteria Reported on Measurement of Tumor Size on CT	No	No	No	No	No
26	Criteria Reported on Measurement of Tumor Size at Surgery	No	No	No	No	No
27	Mortality Reported for Hearing Preservation Cases	Yes (0)	Yes (0)	Yes (0)	Yes (0)	Yes (0)
28	Success Rate (Based on Authors' Criteria)	17/33[b] 9/33[c] W	13/61 W	5/9[b] 3/9[c]	6/25[b] 4/25[c]	8/22 (14/34)[A]

See page 60 for Code for Table 2.

tween HP and tumor size, and three suggested a possible relationship between HP and degree of preoperative hearing loss. None of the 17 authors provided criteria for measuring tumor size, either on computed tomography or at surgery. Thirteen of 17 authors provided data on mortality, with one death reported,[7] which occurred 16 months postoperatively.

Surgical Series. Sixteen reports by 13 primary authors[18-33] are included in Table 2, which uses the

Smith	Sterkers	House	Palva	Samii	Cohen	Gantz	Silverstein	TOTALS
1984[23]	1984[24]	1984[25-27]	1985[28]	1985[29]	1986[30-31]	1986[32]	1986[33]	1982-1986
8	133	56	30	123	27	43	16	492, 77?, 12[A]
Yes	No	Yes	?	No	No	Yes	No	No=7, Yes=5, ?=1
No	No[B]	No	No	No	No[D]	Yes	No	No=10, Yes=3
No	No[B]	No	No[B,E,F]	No	No[D]	Yes	No[E]	No=10, Yes=3
No	No	?	No	No	No	Yes	No	No=7, Yes=1, ?=5
Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	No=1, Yes=12
SO	SO	MF	SO	SO	SO[H]	MF	SO	SO=10, MF=3
Yes	Yes	NA	Yes	Yes	Yes	NA	Yes	No=0, Yes=10, NA=3
No	No	No	No	Yes[K]	Yes[K]	No	Yes[L]	No=7, Yes=6
No	No[B]	No[M]	No	No[M]	No[D]	Yes	Yes	No=9, Yes=4
Implied	Yes	Implied	Implied	No	No	Yes	Implied	No=4, Yes=4, Implied=5
Yes	Yes	Implied	No	Yes	Yes	Yes	Yes	No=2, Yes=8, Implied=3
No	No	No	No	No	No	Yes	No	No=12, Yes=1
No	No[B]	No[E]	No[E,F]	No	Yes	Yes	No[E]	No=7, Yes=6
No	No	No	Yes	No	No	Yes	Yes	No=5, Yes=8
No	No	No	No	No	No	No	No	No=13, Yes=0
No	No	No	Implied	No	Yes	Implied	No	No=10, Yes=1, Implied=2
No	No	No	No	No	No	No	No	No=13, Yes=0
No	Yes[S] (5)	Yes[T] (8)	No	No	Yes[U] (2)	Yes[V] (2)	No	No=6, Yes=7(22)
No	Yes (3 & 3.5 cm)	No	No	No	Yes (3 cm)	No	Yes[W] (3 cm)	No=8, Yes=5(6)
NA	Class 1=3, 2=6 3=10, 5=7	Class 1=13, 2=7 3=4	NA	NA	Class 1=3, 2=6 3=1	Class 1=7, 2=4 3=7, 5=3	NA	Class 1=27, 2=28, 3=28 4=0, 5=17
Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	No=1, Yes=10, ?=2
Yes	No	?	Yes	Yes	?	No	Yes	No=2, Yes=5, ?=6
Yes[X]	No	No	No	No	Yes[Y]	Yes[Y]	Yes[Y]	No=9, Yes=4
No	Yes[Z]	No	No	No	No	No	No	No=12, Yes=1
Yes (0)	No[a]	Yes (0)	Yes (0)	No[a]	No[a]	Yes (1)	Yes (1)	No Mortality=8 Mortality=2
4/8 (6/19 in earlier report)	29/133	24/56[b] 22/56[c]	11/30[b] 9/30[c]	34/123 W	10/27	18/42[b] 21/42[d]	6/16 W	81/195[b] 47/153[c] 185/585[e]

same general format as Table 1. Annotations with Table 2 are explained in the accompanying code. The majority of the authors have written earlier reports, but for the most part, their most recent publications provided all of the data needed for this study. Therefore, although these earlier reports have been reviewed, with three exceptions they have not been referenced. These exceptions are earlier publications by House et al,[25] Brackmann,[26] and Cohen and Ransohoff,[30] which provided substan-

CODE FOR TABLE 2

A. Addendum to paper added 12 more cases to total, but minimal additional data provided.
B. Data limited to patients with hearing preserved.
C. Audiometry limited to speech discrimination only.
D. Data limited to patients with hearing preserved and to some with hearing not preserved.
E. Hearing results stratified rather than individual scores given.
F. Used composite graph with overlapping data.
G. Predominantly middle fossa, but may have used suboccipital in some cases.
H. All cases were done through suboccipūt except one through middle fossa.
I. ABR and direct eighth nerve recording.
J. ABR and compound action potential (CAP), or ECoG.
K. ABR.
L. Direct eighth nerve recording.
M. Data are grouped.
N. Actual data given for patients with hearing preserved; statement simply made that hearing was lost in patients with no HP.

O.

Case	PTA (dB)	SD (%)
1	50 → 32	0 → 92
2	43 → 40	40 → 76
3	45 → 45	60 → 70

P. 18% gain in speech discrimination.
Q. Gain in speech discrimination from 76% to 96%.
R. Gain in speech discrimination from 62% to 76%.

S.

Case	PTA (dB)	SD (%)
1	57 → 57	0 → 100
2	47 → 53	60 → 100
3	57 → 33	0 → 100
4	77 → 72	0 → 20
5	50 → 48	30 → 80

T.

Case	PTA (dB)	SD (%)
1	43 → 50	48 → 80
2	15 → 15	14 → 100
3	62 → 45	44 → 92
4	55 → 25	46 → 100
5	60 → 38	50 → 62
6	20 → 37	70 → 86
7	30 → 42	62 → 88
8	73 → 30	0 → 92

U.

Case	PTA (dB)	SD (%)
1	28 → 8	100 → 92
2	68 → 25	10 → 88

V.

Case	PTA (dB)	SD (%)
1	20 → 5	20 → 100
2	35 → 40	68 → 84

W. Possibility of nonacoustic neuroma being included in series.
X. Measurement is medial to porus acousticus.
Y. Measurement is extension of tumor from porus acousticus.
Z. Measurement includes intracanalicular portion.
a. Mortality results not correlated with HP series.
b. "Measurable hearing."
c. "Serviceable hearing," "useful hearing," "good hearing."
d. Measurable hearing, but no speech discrimination data provided.
e. Total, composite success rate reported by authors of series, based upon their least stringent criteria, and accepting fact that nonacoustic neuromas may be included in some of series.

TABLE 3. CLASSIFICATION FOR HEARING PRESERVATION

Class	*PTA or SRT (dB)**		*Speech Discrimination (%)*
1	0-30	and	70-100
2	31-50	and	69- 50
3	51-90	and	49- 5
4	91-max loss	and	4- 1
5	No response	and	No response

*Use better score. If PTA/SRT score and speech discrimination scores do not qualify for same class, use class appropriate for poorer of two scores.

tive data not available in their most recent papers. The primary reports therefore span the time period between 1982 and 1986.

These series include 492 patients in whom HP was stated to have been attempted, 77 additional papers in which HP may have been attempted, and 12 recently operated patients included as an addendum by Ojemann et al,[22] but with limited data provided.

A significant problem in the analysis of these 13 studies has been the exclusion of tumors other than unilateral acoustic neuromas from this composite series. Bilateral acoustic tumors, with or without other evidence of von Recklinghausen's disease, appear to be a distinct type of tumor as far as cellular growth is concerned.[29,34] We therefore have chosen to exclude from this study those patients having bilateral neuromas, meningiomas, and other cerebellopontine angle tumors that are not unilateral acoustic neuromas. Only five of these 13 studies were limited clearly to unilateral acoustic neuromas. By meticulous analysis of the data in the other eight studies, we have attempted to isolate those patients having unilateral acoustic neuromas and to limit this study to those patients.

Another major problem in assembling the data from these 13 studies for comparison and analysis has been the fact that because of the diversity in type of specialty, orientation, and concepts of the various authors of these studies, the data have been presented in a variety of formats. Audiometric findings frequently have been combined and stratified, and other data have been presented by various grouping and grading arrangements, making it impossible in some cases to compare data from study to study. The ideal situation was to find all of the pertinent data for a particular study listed for each individual patient who was included in that study. In only three instances was this format employed.[20,22,32]

Valid preoperative audiometry for all patients in whom HP was attempted was available in only three of the 13 studies. Five studies gave data for those patients in whom HP was successful, but did not provide complete data for those in whom it was unsuccessful, preventing preoperative classification. Other limitations are indicated by annotations on the code for Table 2.

Preoperative tumor size was reported definitely for all patients in only one study, again making preoperative classification of individual cases impossible except in that one series.[32] Criteria for attempted HP were reported in 12 of the 13 studies.

In ten studies, the suboccipital approach was used, and the middle fossa approach in three. A clear description of the method used to open the IAC was provided in all ten studies using the suboccipital approach.

Surgical monitoring of the eighth cranial nerve was described in six studies using ABR, direct recording from the eighth nerve, electrocochleography (ECoG), or a combination of these. In seven studies, monitoring was not described as being used.

The size of the tumor at surgery in all individual patients operated upon for HP was reported in only four of 13 studies. Problems associated with this particular feature are 1) lack of data for unsuccessful HP cases, and 2) grouping of data (eg, ten patients had tumors ranging from 1 to 3 cm).

Whether or not total tumor removal was accomplished was indicated clearly in four studies and implied in five other studies, but was not specified in the four remaining studies.

Only two studies failed to provide any details on complications.

Only one study[32] provided comprehensive data on facial nerve outcome, in terms of current standards (classification of House and Brackmann[35] or its equivalent). Only four studies provided a complete case-by-case listing of apparently valid postoperative audiometric results, thereby allowing postoperative classification. A variety of limitations to complete results are shown as annotations on Table 2.

Criteria for success in HP are given in eight studies. The use of data processing for data management was not mentioned in any of these studies.

One-year follow-up results were reported in one study and implied in two. No studies presented follow-up results in terms of individual patient satisfaction, including information such as ability to use a hearing aid and freedom from tinnitus or difficulty with balance.

Significant improvement in hearing (15-dB improvement in pure tone average [PTA] or speech reception threshold [SRT] and/or 15% improvement in speech discrimination [SD]) was reported in seven studies for 22 patients. The extent of improvement is shown by annotations on Table 2. The two most striking examples of improved hearing were 1) from 73- to 30-dB PTA and from 0% to 92% SD[25] and 2) from 68- to 25-dB PTA and from 10% to 88% SD.[31]

Hearing preservation in patients having tumors 3 cm or larger was reported in five studies for six patients with tumors ranging from 3 to 4 cm.

Using the classification system shown in Table 3, it was possible to classify 100 patients from six of the studies. Twenty-seven patients were class 1 or excellent hearing (13 of these were in the House series[25-27]), 28 were class 2, 28 were class 3, 0 were class 4, and 17 were class 5 (no audiometric response). The remainder of the patients in the 13 studies could not be classified because of insufficient data.

Ten studies indicated that the authors believed a relationship existed between HP and tumor size, and five between HP and degree of preoperative hearing level. Four studies reported criteria for tumor measurement on CT examination (distance extending beyond the porus acousticus), and one[24] provided criteria for measurement of tumor size at surgery. Ten studies provided mortality data, with two fatalities reported.[32,33]

Line 28 of Table 2 shows the success rate reported for each study. Note that in four studies it was not possible to be certain that the patients being evaluated had only unilateral acoustic neuromas. Note also the variety of criteria used in individual studies. If one takes only those studies[20-28,30-33] clearly limited to unilateral acoustic neuromas that provide evidence of apparently valid postoperative audiometry, and defines success in terms of the least stringent criteria used in the studies, successful HP was reported in 131 patients out of a total of 394, or in 33%.

HEARING PRESERVATION: MEMPHIS SERIES

We have evaluated our own experience in efforts to preserve hearing in patients with unilateral acoustic neuromas.

Materials and Methods. Since 1969, we have treated 160 patients having a diagnosis of unilateral acoustic neuroma; 155 of these were treated surgically. These patients were evaluated initially using audiometric and radiographic techniques. Audiometry has been performed using regularly calibrated audiometers to determine threshold levels for pure tones and speech, and to determine SD scores. Appropriate masking has been used consistently. Radiographic examination has included iophendylate myelography in the early cases, CT beginning in the late 1970s, and magnetic resonance imaging more recently. Preoperative tumor size has been based on the largest diameter of that portion of the tumor medial to the plane of the porus acousticus.

We have systematically collected data on these patients, which have been recorded on specially designed data collection sheets. We have used a Radio Shack TRS-80 Model II microcomputer for data control, d Base-2 software (Ashton-Tate, Torrance, Calif) for data storage and retrieval, and SLM program (Questionnaire Service Co, Lansing, Mich) for analysis.

A classification system was developed that has allowed grading of patients preoperatively and postoperatively according to audiometric scores (Table 4). Table 5 shows the preoperative classification for our 160 patients, and correlates this classification with tumor size. Note that 21 patients had excellent hearing preoperatively, and 13 of these had tumors 2 cm or smaller.

Our criteria for surgery are still under consideration, but are based upon our interpretation of the

TABLE 4. ATTEMPTED PRESERVATION OF HEARING IN ACOUSTIC NEUROMAS (MEMPHIS SERIES)

	CASES	1	2	3	4	5	6	7	8	9	10	TOTALS
	Pre-op Audiometry											
1	PTA (dB)	13	28	52	60	8	30	18	52	37^{M}	7	NA
2	SRT (dB)	-	-	-	60	2	22	20	50	30	2	NA
3	PB Score (%)	50	76	52	76	100	72	92	80	64	100	NA
4	Pre-op Tumor Size by X-ray (In cm or IC) (IC = intracanalicular)	0.5	1.0	IC	0.6	0.5	IC	IC	0.5	2.0^{M}	2.0	IC=3, 0.5-0.6 cm=4 1 cm=1, 2 cm=2
5	Date of Surgery	5/28/70	3/18/71	12/7/72	4/10/80	6/18/81	9/13/84	11/22/85	1/15/86	12/15/86	2/12/87	1970-87
6	Monitoring of VIIIth Nerve Function	No	No	No	No	No	No	Yes^{I}	Yes^{I}	Yes^{N}	Yes^{I}	No=6, Yes=4
7	Surgical Approach (MF = Middle Fossa, SO = Suboccipital)	SO	SO	MF	MF	MF	MF	MF	MF	SO	SO	MF=6, SO=4
8	Tumor Size at Surgery (cm)	0.8	2.0	1.0	1.3	1.0	1.0	0.8	1.0	2.0	2.0	0.8-2.0 cm
9	Total Tumor Removal	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes=10, No=0
10	Surgically Related Death	No	No	No	No	No	No	No	No	No	No	No=10, Yes=0
11	Complications	No	Yes^{A}	Yes^{B}	Yes^{C}	Yes^{D}	No	Yes^{C}	No	Yes^{O}	No	Yes=6, No=4
12	Facial Nerve Function Post-op (John House Classification)	1	5	1	3	1	1	1	1	6^{O}	$?^{Q}$	1=6, 3=1, 5=1, 6=1, $?=1^{Q}$
	post-op Audiometry											
13	PTA (dB) (NR = No Response)	NR	NR	NR	NR	NR	43^{E}	23^{J}	NR	NR	NA^{Q}	NA
14	SRT (dB)	NR	NR	NR	NR	NR	50^{F}	20^{K}	NR	NR	NA^{Q}	NA
15	PB Score (%)	NR	NR	NR	NR	NR	68^{G}	100^{L}	NR	NR	NA^{Q}	NA
16	Post-op Classification (Gardner)	5	5	5	5	5	1	1	5	5	NA^{Q}	1=2, 5=7, $?=1^{Q}$
17	Hearing Improvement Post-op	No	No	No	No	No	Yes^{H}	No	No	No	NA^{Q}	Yes=1, No=8, $?=1^{Q}$
18	Hearing Preservation in 3 cm or Larger Tumors	No	No	No	No	No	No	No	No	No	No	No=10, Yes=0
19	Patients' Subjective Evaluation A = Hearing preserved; patient gratified. B = Hearing preserved; patient neutral. C = Hearing preserved; patient dissatisfied. D = Hearing not preserved.	D	D	D	D	D	A	A	D	D	NA^{Q}	A=2, D=7, $?=1^{Q}$
20	Length of Follow-up (months)	5	63	168	53	50	25^{P}	13^{P}	8	2	1	1-168 months

CODE FOR TABLE 4

A.	Facial paralysis; required anastomosis of nerves VII and XI and multiple procedures to protect eye.
B.	CSF leak; required revision surgery with no further problem.
C.	Facial paralysis; spontaneous recovery.
D.	CSF leak; required two secondary procedures, with no further problem. Lost facial function, but returned to normal spontaneously. Had mild speech aphasia following middle fossa surgery, which recovered completely by eighth postoperative day.
E-G.	Follow-up audiometry showed sustained HP. Scores at 2 years 1 month postoperatively were as follows: PTA, 43 dB; SRT, 30 dB; PB, 88%.
H.	Speech discrimination improved from 72% preoperatively to 88% postoperatively.
I.	Hearing monitored surgically with ABR.
J-L.	Follow-up audiometry showed sustained HP. Scores at 1 year 1 month postoperatively were as follows: PTA, 21 dB; SRT, 15 dB; PB, 92%.
M.	Surgery performed on better hearing ear (with Meniere's disease in opposite ear). Patient had been followed nonsurgically for 4 years, by which time serial CTs showed significant growth of tumor.
N.	Hearing monitored surgically with ABR and with direct stimulation of eighth nerve.
O.	Facial paralysis, not yet recovered 2 months postoperatively.
P.	Hearing preserved, with good function, in two of ten cases.
Q.	Data unavailable for one patient because of short period of follow-up.

data presented in Table 2. If a patient has a tumor of 2 cm or less, and hearing is in the upper range of class 3 (Table 3) or better, and the patient is a suitable candidate in terms of general health and prefers that we attempt HP, we will probably do so. If the tumor is intracanalicular, or extends no further than 0.5 cm into the cerebellopontine angle, and the patient is not elderly, we prefer the middle fossa approach; otherwise, we prefer the suboccipital approach.

When we use the middle fossa approach, we use the method originally developed by William House.[36] When we use the suboccipital approach, we employ the traditional neurosurgical technique, but in addition use a surgical drill with continuous suction and irrigation to remove bone from over the posterior surface of the IAC in order to allow access to that portion of the tumor. We are conservative in the removal of bone as we approach the lateral end of the canal and attempt to avoid entry into the structures of the labyrinth.

Regarding surgical technique in actual tumor removal, since the early 1980s we have emphasized use of the carbon dioxide laser in order to minimize manipulation of anatomic structures.[37]

Tumor size is estimated at surgery, and at the present time we are influenced strongly in this estimate by the measurement of the tumor preoperatively by CT or MRI.

Results. Of 155 patients undergoing surgery for removal of unilateral acoustic neuromas, ten were operated upon with the intent of trying to preserve hearing. The data resulting from our experience with operating upon these ten patients are shown in Table 4. Annotations are explained in the accompanying code.

TABLE 5. PREOPERATIVE CLASSIFICATION FOR HEARING PRESERVATION

		*Tumor Size**		
Class	*Number of Patients*	*≤2 cm*	*>2 cm*	*Cannot Determine*
1	21	13	8	0
2	27	18	6	3
3	50	38	7	5
4	4	3	1	0
5	58	22	31	5
Totals	160	94	53	13

*Preoperative assessment based on x-ray study.

The preoperative audiometric scores are shown on lines 1 through 3, and the preoperative tumor size on line 4. Note that patient 9 had Meniere's disease in the opposite ear, with hearing worse than in the ear having the tumor. He therefore was treated nonsurgically for 4 years 4 months and received streptomycin intermittently for control of dizziness believed to be the result of Meniere's disease. He has been reported upon previously as a nonsurgical patient.[38]

The time span of this study is from 1970 to 1987. Our failure to accomplish HP in our earlier experience lessened our enthusiasm for this procedure until more recently, when evidence began to accumulate in the literature that HP was a practical concept.

We did not use surgical monitoring until case 7, when we began to use ABR during surgery. Currently we are directly stimulating the eighth cranial nerve as well, and plan to use ECoG monitoring in future cases.

We have used the middle fossa approach on six patients, the suboccipital on four. No tumor has been estimated as being larger than 2 cm at the time of surgery. Total removal has been accomplished in all cases, and no deaths have occurred in this series. Complications have included CSF leakage in two patients and facial weakness or paralysis in three patients. Details are provided on line 11. Facial nerve outcome using the classification system of House and Brackmann[35] is shown on line 12.

Postoperative audiometric results are shown on lines 13 through 15. Two of our most recently operated patients have retained hearing, and their results are class 1 according to the classification system shown in Table 3. One of these patients demonstrated improvement in hearing, with speech discrimination improving from 72% preoperatively to 88% 2 years 1 month postoperatively.

Line 19 (Table 4) provides a classification system for the patients' postoperative subjective evaluations of the effects of surgery. Two of our patients rate their surgical outcome as class A, are gratified with their results, and have no problem with dizziness or tinnitus.

With one exception, all patients either have been followed for at least 4 years, or are currently under follow-up, but for a shorter duration of time since surgery.

DISCUSSION

In a study such as this in which it has been necessary to interpret large amounts of data of widely varying types, and on occasion to make subjective judgments of those data, the likelihood of occasional error on our part is readily apparent. We regret this, but believe that the value of subjecting these various studies to a comparative analysis justifies the risk of occasional error.

Feasibility of Attempting Hearing Preservation. Clemis[39] discussed the feasibility of HP and concluded that even with sophisticated diagnostic techniques, only a small percentage of acoustic tumor patients are suitable candidates for attempted HP.

Neely[40] and Luetje et al[41] pointed out the tendency of acoustic neuromas to involve the substance of the cochlear nerve peripheral to the apparent (visual) margin between tumor and nerve, and concluded that this histologic feature may prove to be a significant limitation upon our efforts to accomplish HP successfully over the long term.

Tos and Thomsen[42] concluded that because the morbidity and mortality associated with the suboccipital approach are greater than with the translabyrinthine approach, they did not advocate attempting to preserve hearing.

In spite of these concerns, there is obviously a strong trend in neurotologic surgery toward attempting the preservation of hearing. And in spite of the numerous instances of data that are either unavailable for review or of uncertain value in the present study, there is an ample body of well-documented cases in which hearing clearly has been preserved successfully without apparent adverse effect upon the patients.

Patient Selection. Data in Table 2[19,24,29] suggest a tendency by some who use the suboccipital approach to attempt HP with very few limitations having to do with preoperative level of hearing or tumor size being applied to surgical candidacy. Gantz et al[32] have not used the preoperative level of hearing as a criterion for surgery, and have attempted to preserve even minimal hearing function. Others appear to be more selective in identifying surgical candidacy,[20,23] although surgical criteria are quite variable from study to study.

In spite of the importance of the level of hearing and tumor size, other factors such as hearing in the opposite ear, age, health status, and the wishes of the patient tend to make patient selection for surgery a highly individualized process.

Data. There are very few examples in Tables 1 and 2 of comprehensive reporting of data pertinent to HP, the report of Gantz et al[32] being by far the best example. The problems that appear to have occurred include allowing data on HP for unilateral acoustic neuromas to become mixed with other types of data, with resulting confusion. Perhaps the greatest problem is the simple failure to collect the appropriate data and display them clearly and unambiguously. Articles from the neurosurgery literature, with few exceptions, either omit audiometric data or present data that are flawed.

Until there is a generally accepted set of standards for this subject, and until basic questions have been answered, it is advantageous to avoid grouping of data, but rather to report a full range of data for all patients in whom HP is attempted. Otherwise it becomes extremely difficult to compare data from study to study and to make correlations between types of data. Jannetta et al[20] reviewed this same literature and came to similar conclusions.

It is of interest to review the data on line 22 of Table 2, in which patients for whom there are sufficient data are graded postoperatively according to the criteria in Table 3. Note that of the 27 patients from all of the studies who achieved a class 1 score, 13 (48%) were from the series of House et al,[25-27] and seven (26%) were from the Gantz et al[32] (Iowa) series. Both of these studies use the middle cranial fossa approach exclusively.

The percentage of properly selected patients who actually may achieve HP is stated frequently to be approximately 50%.[18] To test this assumption, we have selected the cases from those studies[20-28,30-33] listed in Table 2 for which valid-appearing postoperative audiometric results are available, with success defined in terms of the least stringent criteria used in these studies. Our own series (Table 4) also qualifies. The total number of patients in these series is 404; 133 of them (32.9%) retained hearing.

Instances of HP in patients having very large tumors have been reported in the literature in the past and reference subsequently made to these reports both in scientific papers and in statements before scientific groups. We believe it is unfortunate that so many of these reports have not been subjected to a greater degree of scientific scrutiny prior to initial publication. It would seem to be reasonable to insist that a report dealing with HP in acoustic neuroma surgery should be supported by evidence of properly performed pure tone and speech audiometry using appropriate masking, both preoperatively and postoperatively. Follow-up studies for at least a year also would seem to be reasonable. In reviewing the data contained in Table 1, it would appear that except for case report 16, and perhaps 9, all other reports in Table 1 describing HP in cases of tumors 3 cm and larger should be viewed skeptically for lack of audiometric documentation. These two documented cases describe tumors of 3 cm and 4 to 5 cm in size. In Table 2, only studies 19, 22, and 30-31 describe successful and well-documented HP in the presence of large tumors (4 cm, 4 cm, and 3 cm). It would appear from this analysis that among the studies reviewed, there have been only five well-documented instances in which hearing has been preserved in patients having tumors 3 cm or larger, the largest being 4 to 5 cm.

Criteria and Classification. McCabe[43] recently has described an ideal classification system for Meniere's disease as one that is "simple, straightforward, and most of all can be *remembered* without looking it up." Such a system for preoperative and postoperative grading of acoustic neuroma patients should also be comprehensive enough to include the hearing levels that are of clinical value.

Wade and House's[27] 50/50 rule for serviceable hearing indicates a PTA or SRT of 50 dB or better and an SD score of 50% or better. Although straightforward and easy to remember, it does not distinguish the various levels of hearing that are of clinical interest.

Silverstein et al[33] have proposed a classification system that appears to meet all of the above requirements. We found this system useful, modified it slightly, and used it for this study (Table 3). Although useful in classifying level of hearing both preoperatively and postoperatively, until a universally accepted system is available, such a grading system does not take the place of a case-by-case reporting of actual audiometric scores.

Recommendations. Based upon our own experience as well as our review of the reports of others, we believe that future reports of efforts to preserve hearing in acoustic neuroma surgery should include each of the items listed in the first column of Table 2. We further recommend that the actual scores obtained at the time of preoperative and postoperative audiometric testing be reported for each patient in a given study, with indication that conventionally accepted audiometric standards, including appropriate masking, have been employed. Because of the problems associated with storage and management of large amounts of data, we recommend the use of data processing for this purpose.

We feel that classification of patients preoperatively and postoperatively by degree of hearing loss is also clinically useful, and we recommend a system similar to that of Silverstein et al[33] or the modified system shown in Table 3.

We also believe it is important to report patients' subjective assessments of postoperative hearing, which after all is the ultimate criterion for surgical success.

CONCLUSIONS

Studies have been reviewed that reported 585 patients in whom HP was attempted; HP was claimed in 185 of these (31.6%). It was reported for 36 additional patients in case reports for which the total number of patients is not available. There appear to be, therefore, claims made in this literature for HP in 221 patients out of 621 + patients in whom it was attempted.

When limited to patients having unilateral acoustic neuromas with apparently valid postoperative audiometric findings, and accepting the varying criteria of success for the different authors, there remains a series of 394 + cases, in whom HP was achieved in 131.

We conclude 1) that HP is a reasonable goal in unilateral acoustic neuroma surgery, although the number of available candidates is relatively small; and 2) that intelligent selection of patients and high quality surgical technique are the keys to success.

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MORPHOLOGIC EFFECTS OF GLYCEROL AND UREA ON COCHLEAR TISSUES OF THE CHINCHILLA

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Glycerol and urea are used as test agents in confirming the diagnosis of endolymphatic hydrops. Although both substances act as osmotic diuretics, recent evidence suggests that they may have differing physiologic effects on the inner ear. This study was designed to compare the morphologic effects of urea and glycerol on cochlear tissues, using the chinchilla as an experimental model. Animals were given subcutaneous injections of glycerol (2 g/kg) or urea (1.2 g/kg) over periods of 3 hours, 4 days, or 1 week. Both agents were found to produce ultrastructural changes, including spiral ligament vacuolization, intracellular alterations of the stria vascularis, and increased numbers of Hensen's bodies in outer hair cells. These alterations appeared indicative of metabolic stress, but not toxicity. The morphologic findings provided no evidence that glycerol and urea affect the inner ear by fundamentally different mechanisms of action.

KEY WORDS — cochlear morphology, glycerol, Meniere's disease, urea.

INTRODUCTION

In 1861 Meniere[1] first attributed the symptom complex of fluctuant sensorineural hearing loss, tinnitus, and incapacitating episodic vertigo to a disorder of the inner ear. This symptom complex, now known as Meniere's disease, is associated with an abnormality in the production and/or absorption of endolymph within the inner ear, resulting in endolymphatic hydrops.[2] In spite of many years of research effort, the causation and treatment of this condition remain matters of vigorous speculation and debate.

Glycerol and urea currently are used as test substances in confirming the diagnosis of Meniere's disease.[3] These agents increase serum osmolality, thereby producing an osmotic gradient between the blood and inner ear fluids.[4,5] This osmotic effect is believed to bring about a reduction of endolymph volume, which provides a temporary improvement in auditory function.[3,6] Urea presently is becoming the more popular of the two agents for clinical testing and long-term therapy, since it seldom produces the headache and nausea often associated with glycerol administration.[7,8]

Although experimental animal studies have shown that urea and glycerol produce similar osmotic changes in serum and perilymph,[4,5] clinicians frequently find that patients who respond positively to glycerol fail to do so with urea and vice versa.[3] Also, with both substances, positive test results are not always well correlated with increased serum osmolality,[3,8] a finding which suggests that osmotic effects alone may not account for the observed functional changes.

Glycerol is a potentially important metabolic substrate that may serve as a precursor for synthesis of membrane phospholipids and as an energy source through glycolysis.[9,10] Urea, on the other hand, is an end product of protein metabolism normally excreted in the urine. Nishimura and Tachibana[9] have demonstrated that glycerol introduced into the perilymph of guinea pigs is incorporated into outer hair cells where it can be autoradiographically localized in the area of the subsurface cisternae adjacent to the cell membrane. Glycerol therefore may play an active role in inner ear metabolism and exert physiologic effects different from those of urea. If glycerol and urea do affect the cochlea in different ways, they might be expected to produce different structural alterations in inner ear tissues.

The present study was designed to compare the morphologic effects of urea and glycerol on cochlear tissues using the chinchilla as an experimental animal model. The agents were administered by subcutaneous injection at relatively low dosage levels, and animals were evaluated after either single or multiple injections of the two substances.

METHODS

Eighteen young adult chinchillas served as experimental animals in this study. Nine of these received glycerol; the other nine animals were given urea. Both agents were administered by subcutaneous injection in a 50% solution of sterile saline. The animals were divided into groups of three and given glycerol or urea over time periods of 3 hours, 4 days, or 1 week. Animals dosed for 4 days and 1 week received injections twice per day (morning

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SUMMARY OF FINDINGS (N = 18)

Survival Time	*Proliferation of Hensen's Bodies*		*Strial Cell Volume Changes*		*Intracellular Changes in Strial Cells*		*Vacuolation of Spiral Ligament*	
	Glycerol	*Urea*	*Glycerol*	*Urea*	*Glycerol*	*Urea*	*Glycerol*	*Urea*
3 hr	+	0	+	0	+	+	0	0
	0	0	0	+	+	+	+	0
	+	+	+	+	+	+	0	+
4 d	0	+	+	+	+	+	+	0
	+	+	0	0	+	0	+	+
	+	+	0	+	0	+	0	+
1 wk	+	+	+	0	+	+	+	+
	+	+	+	0	+	0	+	+
	0	0	+	+	+	+	0	0

Columns under each of four categories show presence (+) or absence (0) of indicated change, relative to control animals, in each of glycerol and urea animals.

and evening) and were killed for histologic study 3 hours after the last dose. The remaining animals were killed 3 hours after a single injection of glycerol or urea. The amount of glycerol given per dose was 2 g/kg; urea was administered at a dosage of 1.2 g/kg. These dosages were chosen so as to provide equimolar (0.02 mol/kg) quantities of the two agents and were equivalent to approximately 1.3 to four times the amounts used per dose in previous clinical studies.

Three control animals received subcutaneous injections of 1.5 mL 0.9% saline on the same dosage schedule as the experimental group. (One saline control animal was injected at each of the three time periods, ie, 3 hours, 4 days, and 1 week). Inner ear tissues from another group of five normal chinchillas provided additional control material. Tissues from the experimental animals, animals receiving saline, and normal animals all were processed by the same methods.

At the time temporal bones were taken for histologic examination, the animals were anesthetized with ketamine hydrochloride and killed by decapitation. The middle ear cavities were opened quickly to permit fixation of inner ear structures by perilymphatic perfusion with 1% osmium tetroxide in Veronal acetate buffer at pH 7.4. After 1 hour in osmium, the specimens were rinsed in 50% ethyl alcohol, in which they were stored until further processing.

Cochlear tissue specimens were obtained by microdissection and prepared for either light or electron microscopy. For light microscopy, surface preparations or 1-μm sections cut from plastic-embedded material were used. Tissues prepared for electron microscopy were dehydrated in ethanol and propylene oxide and embedded in Medcast Epon (Ted Pella, Inc, Tustin, Calif) using routine methods. Thin sections were obtained from selected portions of the specimens and impregnated with uranyl acetate and lead citrate before transmission electron microscopy.

RESULTS

No changes in the position of Reissner's membrane were detected during microdissection of temporal bones from animals given glycerol or urea. There was therefore no indication of reduced endolymph volume following administration of either agent. Ultrastructural study of the stria vascularis and organ of Corti did, however, reveal signs of physiologic stress in these tissues, as described below. In general, glycerol and urea were found to produce similar changes that did not appear to increase in severity with multiple dosage. That is, the alterations present 3 hours after a single dose were essentially the same as those observed after 4 days or 1 week of diuretic administration. The Table shows the numbers of animals having the various types of alterations observed at each of the three time periods used in the study.

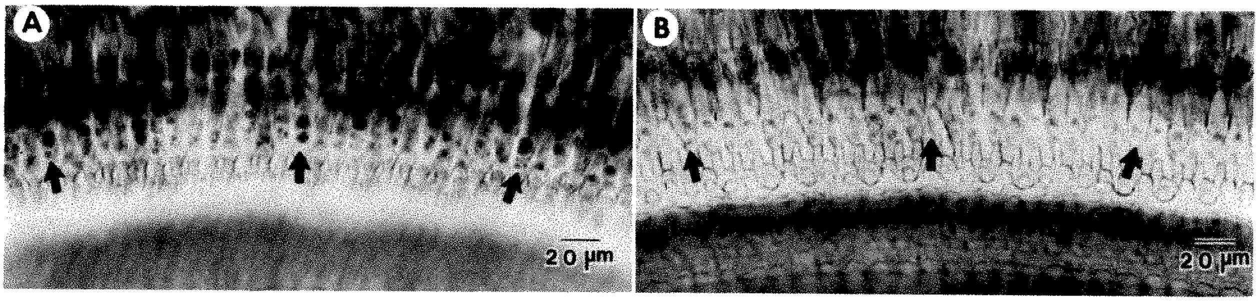

Fig 1. Surface preparations of organ of Corti showing increase in size and number of Hensen's bodies in outer hair cells. A) Experimental animal that received glycerol for 1 week. Arrows indicate second row hair cells in which Hensen's bodies (seen as dark, roundish structures) are especially prominent. B) Control animal. Arrows indicate cell bodies of second row outer hair cells; no Hensen's bodies are visible.

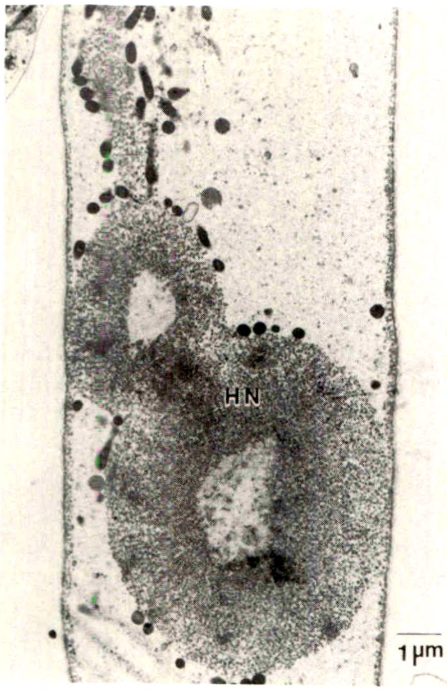

Fig 2. Electron micrograph showing enlarged Hensen's bodies (HN) in outer hair cell of chinchilla killed 3 hours after single subcutaneous injection of glycerol.

Cochlear hair cell loss was not found in any of the experimental animals. However, after application of both agents, there was an increase in the size and number of Hensen's bodies (whorled tubulovesicular structures thought to be in continuity with the subsurface cisternae[11]) in outer hair cells of the apical cochlear turn. Although small numbers of these structures were observed in control material, they were difficult to detect by light microscopy in normal specimens. However, in experimental material, large osmiophilic Hensen's bodies were obvious in whole mount preparations of the organ of Corti (Fig 1). The enlarged Hensen's bodies often nearly filled the cross-sectional diameter of individual hair cells, and several of these whorled organelles were typically present in each sensory cell (Fig 2). As indicated in the Table, proliferation of Hensen's bodies was observed in 12 of the 18 experimental animals included in the study and the phenomenon was seen at all three time periods.

Relative to controls (Fig 3), the experimental specimens tended to show decreased volume of the marginal cells in the stria vascularis. As shown in Fig 4, the marginal cells appeared shrunken, with the basal portions of the cells seemingly compressed between adjacent intermediate cells. The extensive interdigitation normally seen between marginal and intermediate cells also was markedly reduced. No increase in intercellular space between the two types of cells was found, and there was no evidence of extracellular fluid accumulation in any portion of the stria vascularis. Marginal cells with a shrunken or compressed appearance were present in all cochlear turns at all three time periods employed in the study, and the effect was observed in 11 of the 18 experimental animals. Although this morphologic change was found after administration of both glycerol and urea, it was seen more distinctly in animals given glycerol.

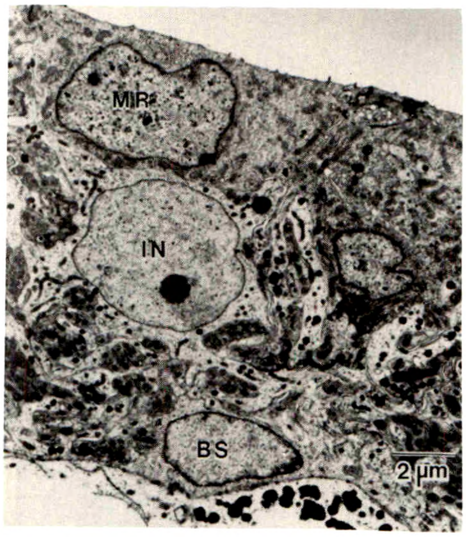

Fig 3. Normal chinchilla stria vascularis. Melanocyte process containing melanin granules underlies basal cell (BS). MR — marginal cell, IN — intermediate cell.

Intracellular changes also were found in the strial marginal cells. Irregularly shaped patches of light ground substance typically were seen in the marginal cells of experimental animals (Fig 5A,B), but were absent in control material. A delicate, flocculent substance often was detectable in these electron-lucent areas, which were usually present in the apical portions of the cells near the endolymphatic surface of the stria. In some specimens, a fine-grained particulate material of medium density was observed within the light patches. The patches of light ground substance were also visible by light microscopy in 1-µm sections, in which they stained metachromatically with toluidine blue.

Dense bodies 0.5 to 2 µm in diameter were seen frequently in the marginal cell cytoplasm, often within or near the light patches. These bodies contained a very electron-dense particulate material in which small droplets of a lighter substance, probably lipid, sometimes were seen (Fig 5C). In surface preparations, these structures showed a golden brown color like that of melanin. By electron microscopy, they had the general appearance of lysosomes. However, careful study failed to reveal a limiting membrane bounding the dense bodies. These organelles were observed occasionally in control material, but they were much more numerous in marginal cells of animals given glycerol or urea.

The marginal cells of experimental animals also showed an increase in large, clear vesicles (probably primary lysosomes), which were most abundant in the stria of the apical cochlear turn (Fig 5D). Numerous small, lined vesicles were present in the

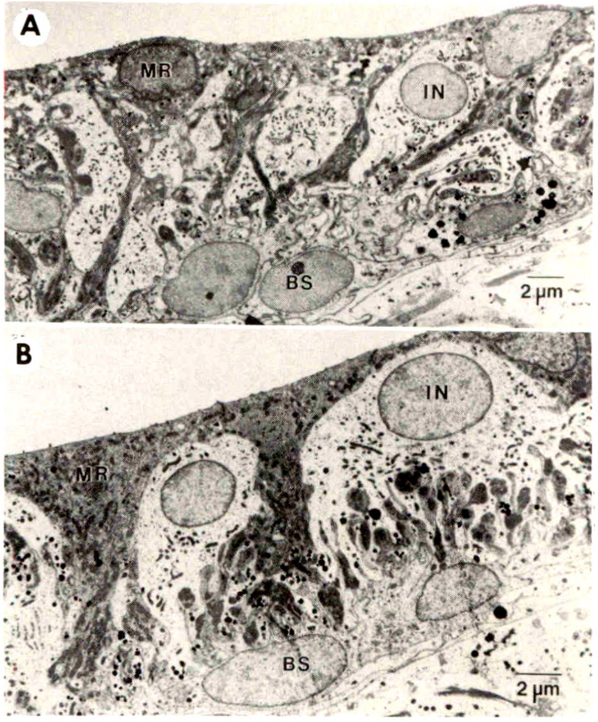

Fig 4. Cross sections of stria vascularis showing shrunken marginal cells (MR) after glycerol administration. A) Apical turn, 3 hours after single glycerol injection. B) Basal turn, after 1 week of glycerol administration. IN — intermediate cell, BS — basal cell.

marginal cell cytoplasm near the endolymphatic surface of the stria, but their numbers were not markedly greater than in control material.

The tight junctions between strial marginal cells appeared completely intact in the experimental specimens. No evidence of widened junctions or bubble formation within the junctional complexes was observed.

As described above, the intermediate cells tended to lose their interdigitating processes with marginal cells and to assume a somewhat expanded appearance — a change that was especially evident in animals that received glycerol. In addition, the intermediate cells showed increased amounts of rough endoplasmic reticulum and more numerous lipid droplets in their cytoplasm. Stacks of ribosome-studded endoplasmic reticulum like those illustrated in Fig 6A were prominent and frequently observed intracellular structures in intermediate cells from experimental specimens, but were rarely found in control material. Lipid droplets, which in osmium-stained preparations were seen as jet black spherical droplets, also were noted in intermediate cells following glycerol or urea administration (Fig 6A), but were never observed in control specimens.

Some experimental animals also showed unusually large numbers of osmiophilic lipid droplets scattered throughout the spiral ligament, and many such droplets were seen in the basal cells of the stria as well. An unequivocal increase in lipid deposition in these locations was difficult to establish, however, since large variations in the amount of lipid material in the basal portion of the stria and in the spiral ligament were seen in controls.

Although there were also wide variations in melanin content of the stria vascularis in the control animals, there did appear to be, on average, an increase in electron-dense material with the ultrastructural appearance of melanin in both intermediate and basal cells following urea and glycerol application. This was particularly evident in basal cells, which often contained large, membrane-bound clusters of dense granules (Fig 6B). These structures were strikingly similar in morphology to the so-called melanosome complexes described in the skin, in which melanin granules are broken down by the action of lysosomal enzymes.[12]

Ten of the 18 experimental animals showed vacuolization of the spiral ligament immediately adjacent to the stria vascularis near the area of Reissner's membrane attachment (Fig 7). This alteration occurred only in the apical cochlear turn and appeared to be due to formation of large intracellular vacuoles in the spiral ligament cells. As illustrated in Fig 7A, the vacuolization was sometimes so severe that the stria was visibly displaced inward into the scala media.

No abnormalities were observed in the spiral prominence epithelium or spiral ligament behind the prominence in the experimental material. There were also no consistent changes in the endothelial cells or basement membranes of strial or spiral ligament capillaries in animals that received glycerol or urea.

DISCUSSION

Several investigators have studied the time course and magnitude of osmotic changes in serum, CSF, and perilymph after administration of glycerol and urea in experimental animals.[4-6] There have been few published reports, however, on morphologic changes produced by these agents. The most extensive anatomic studies have been done by Duvall et al[13] and Duvall and Hukee,[14] who described structural alterations in the chinchilla stria vascularis after single intravenous injections of large doses of glycerol and urea (6 g/kg glycerol; 4 g/kg urea). Swelling of marginal cells and strial edema were reported following administration of both agents. In animals killed 30 seconds after injection of glycerol, collapse of Reissner's membrane was found, and at intervals of 10 minutes to 3 hours there was scalloping of marginal cell surfaces and extensive edema of the stria.

In a more recent morphologic study using intraperitoneal (rather than intravenous) administration, Duvall et al[15] found strial edema and variable marginal cell swelling 1, 2, and 3 hours after injection

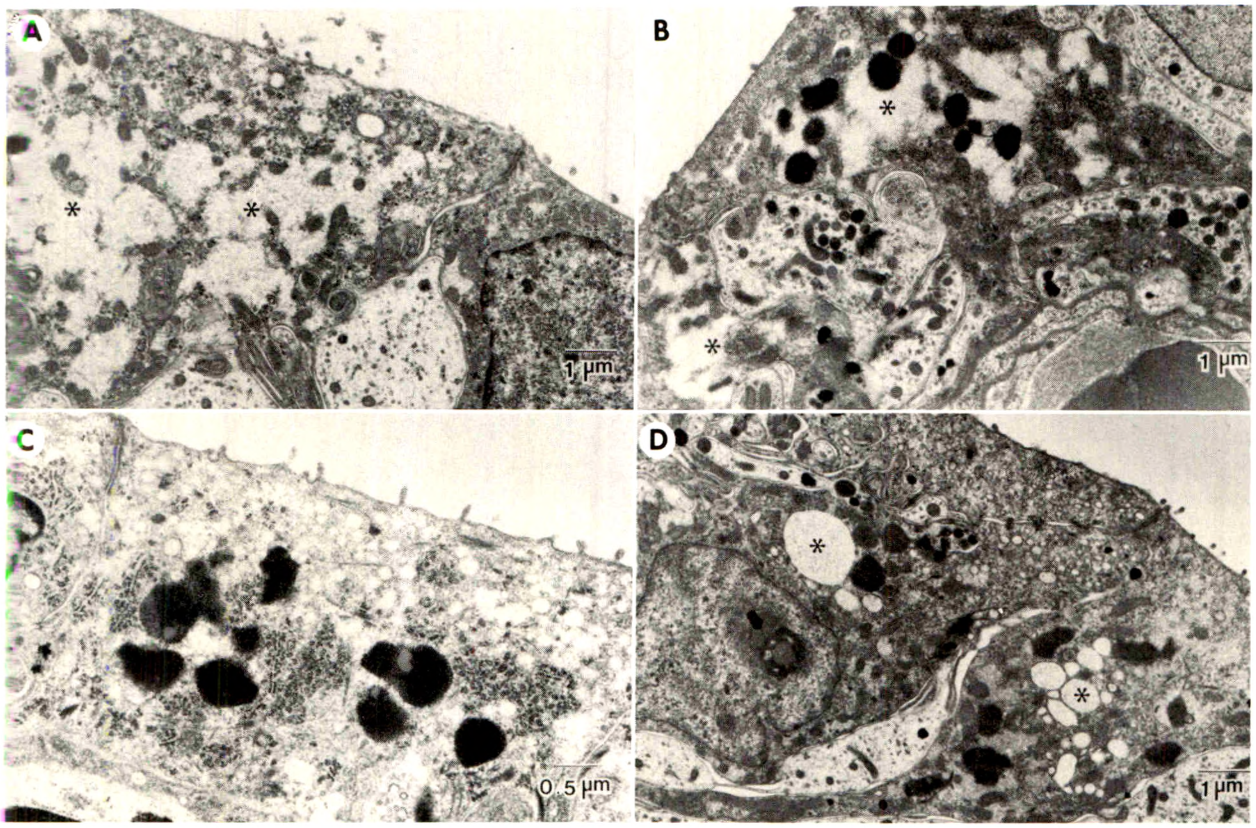

Fig 5. Strial marginal cells after glycerol and urea administration. A) Glycerol dosage for 4 days. B) Three hours after single injection of urea. Patches of light ground substance are indicated by asterisk in A and B. Note dense, lysosome-like bodies associated with patches of light marginal cell cytoplasm. C) Dense bodies are surrounded by rough endoplasmic reticulum in marginal cell from animal given urea for 1 week. D) Large, membrane-bound vesicles (asterisks) in marginal cells of apical cochlear turn from animal killed after 4 days of glycerol administration.

of 6 g/kg glycerol. No obvious collapse of Reissner's membrane was observed in cochlear cross sections. However, morphometric studies of the cross-sectional area of the scala media did reveal a statistically significant decrease in scala media volume at the 1-hour and 3-hour time periods.

With the lower dosage levels and subcutaneous route of administration used in the present study, the marginal cells were found to be shrunken at 3 hours after injection of both glycerol and urea, and there was no evidence of strial edema in any of the experimental animals. These findings illustrate that quite different results are obtainable with changes in dosage and route of administration — a fact that unfortunately complicates efforts to clarify the detailed mechanism of action of osmotic diuretics under the conditions of their use in clinical testing.

Along with marginal cell shrinkage, a variety of intracellular alterations were noted in lateral wall structures in this study. Some of these, such as increased pigmentation of the stria, patches of light ground substance in marginal cells, and vacuolization of the spiral ligament, also have been described following noise exposure[16-18]; such alterations generally are believed to result from metabolic stress due to overstimulation of cochlear tissues.

The intermediate cells of the stria also showed signs of heightened activity, as evidenced by moderate swelling of the cells, increased amounts of rough endoplasmic reticulum, and accumulation of intracellular lipid droplets. The intermediate cells did not show cytoplasmic vacuolization, mitochondrial damage, clumping of nuclear chromatin, or other changes indicative of degeneration. They also showed no such changes in animals given repeated doses of the osmotic agents for periods of up to 1 week. Thus, the increase in intermediate cell volume first observed at 3 hours did not appear to represent an early stage of degeneration. It is of interest to note that Santi et al[19] described moderate swelling of intermediate cells 10 minutes after intravenous injection of mannitol in chinchillas. The animals also showed shrinkage of strial marginal cells and marked edema of the intercellular spaces. These changes all appeared to be reversible, since strial specimens appeared normal 24 hours after mannitol injection. It is well known that intermediate cells are severely damaged or completely destroyed following intense noise exposure or application of loop-inhibiting diuretics.[11,20] Administration of osmotic diuretics at relatively low dosages appears to be one of the very few experimental manipulations that results in increased activity of intermediate cells without obvious toxicity — a finding that eventually may prove useful in un-

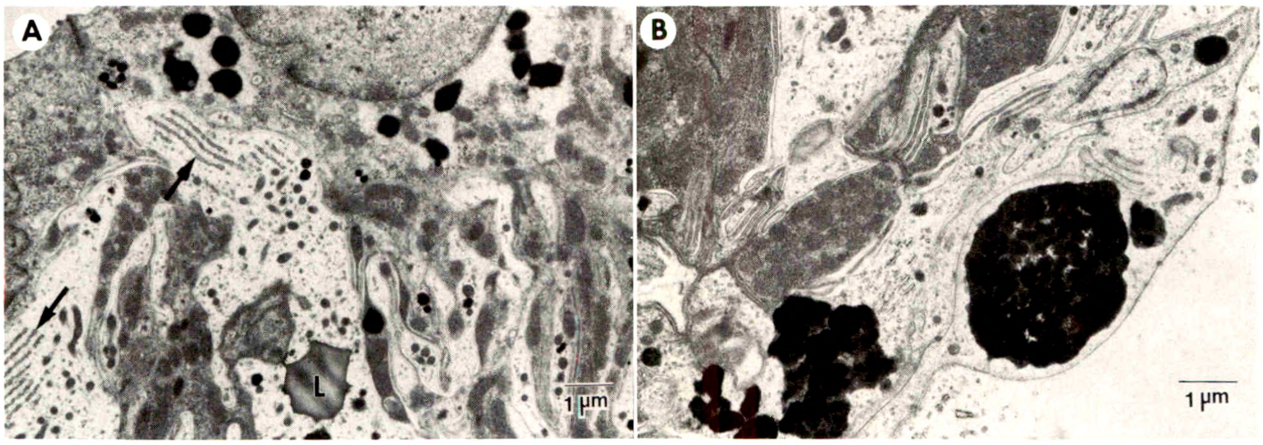

Fig 6. Intermediate and basal cells 3 hours after single glycerol injection. A) Lipid droplet (L) and rough endoplasmic reticulum (arrows) in intermediate cell processes and B) clusters of melanin granules in strial basal cells.

derstanding the functional role of this cell type.

A somewhat unexpected effect of glycerol and urea administration was the alteration of Hensen's bodies in the organ of Corti. Both agents were found to produce an increase in the size and number of Hensen's bodies in outer hair cells of the apical cochlear turn. As with the strial changes noted above, this phenomenon has been observed in conjunction with noise exposure.[21,22] Proliferation of Hensen's bodies also has been reported following disruption of cochlear fluid balance due to experimental endolymphatic hydrops[23] or to intermixing of perilymph and endolymph after surgical rupture of Reissner's membrane.[24]

The alterations described above were observed to occur within the relatively brief time period of 3 hours after injection of urea or glycerol. This is consistent with previous reports that changes in intracellular organelles may occur within minutes following systemic administration of hyperosmotic agents. For example, Duvall and Hukee[14] noted an increase in intracellular membranous material, microfilaments, and endoplasmic reticulum in strial marginal cells 30 seconds after an intravenous infusion of glycerol requiring 12 to 13 minutes. Glycerol also has been shown to be incorporated into the lipid constituents of cell membranes in brain tissue within 15 minutes of its administration.[25]

In this study, glycerol and urea were found to produce essentially identical anatomic alterations. There was therefore no evidence that the two substances affect the inner ear by fundamentally different mechanisms of action. Furthermore, urea and glycerol did not appear to be toxic at the dosages used, since frank degenerative changes were not observed, even after twice daily administration of the two diuretics for periods of up to 1 week. As noted above, Duvall et al[15] found swollen marginal cells, strial edema, and reduced endolymph volume 1 to 3 hours after intraperitoneal injection of 6 g/kg of glycerol in chinchillas. However, at 5 hours after injection, the marginal cell surfaces appeared normal, strial edema had disappeared, and the volume of the endolymphatic space had returned to normal. Thus, the cochlear tissues appear to have the capacity to recover quickly from the effects of large doses of osmotic diuretics. In the present study, which employed lower doses, the observed morphologic changes were relatively mild; it therefore seems reasonable to expect that there was time for considerable recovery between doses (which were spaced 10 to 12 hours apart in the 4-day and 1-week animals), so that no significant cumulative effects occurred.

In general, the results of the present study support the notion that increased metabolic demand is imposed on tissues of the inner ear following administration of osmotic diuretics. It is well established that glycerol and urea produce changes in osmolari-

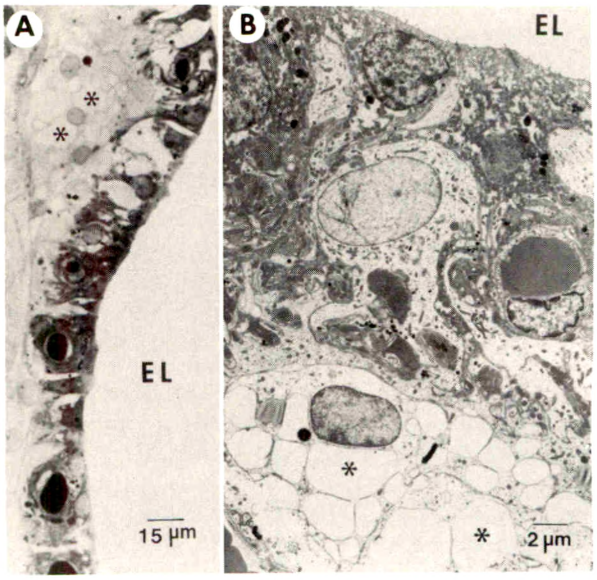

Fig 7. Intracellular vacuolization of spiral ligament of apical cochlear turn following glycerol administration. A) One-micron section showing displacement of upper portion of stria vascularis into endolymphatic space (EL). Large vacuoles in spiral ligament are marked by asterisks. B) Electron micrograph showing vacuoles (asterisks) in spiral ligament cell immediately adjacent to stria.

ty of the serum and perilymph,[4,5] and there is some evidence that these changes bring about fluid shifts between the various compartments of the inner ear.[14,15] Such a disturbance of fluid balance would be expected to provoke increased activity of the fluid regulatory tissues in an effort to maintain endolymphatic homeostasis. Another factor likely to influence metabolic activity is increased oxygen supply. Substances that elevate serum osmolarity are known to increase blood flow in the brain and other organs.[10,26] In the inner ear, Prazma[27] has in fact demonstrated increased endocochlear oxygen concentration following glycerol administration in experimental animals. Because of their osmotic properties, both glycerol and urea may therefore improve conditions for oxidative metabolism in the membranous labyrinth — a factor of possible significance in accounting for the functional effects of these agents.

Given the information available at present, it seems clear that further research will be necessary in order to determine how the various morphologic changes observed in this and previous studies may be related to the functional changes seen clinically after administration of glycerol and urea. Although it is widely believed that reduction of endolymph volume is a major factor underlying improved hearing in patients who receive osmotic diuretics, the relative contributions of possible fluid shifts across the stria vascularis, Reissner's membrane, and epithelia of the endolymphatic duct and sac have yet to be determined. Attempts to explain changes in endolymph volume solely on the basis of changes occurring in the stria must therefore be approached with considerable caution. Furthermore, it is now apparent that the types of changes seen in the stria in experimental animals depend significantly on dosage and route of administration of osmotic diuretics, making it all the more difficult to predict how the strial cells might react in human patients who have impaired inner ear function associated with endolymphatic hydrops.

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Ann Otol Rhinol Laryngol 97:1988

ELIMINATING THE TOYNBEE PHENOMENON IN PATIENTS WITH NASAL PACKS

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Nasal packing is a common procedure in otolaryngology, but is not a completely innocuous procedure. Besides aggravating mouth breathing, complete nasal obstruction results in an annoying Toynbee phenomenon. In patients with bilateral anterior nasal packing, we recorded high pressure gradients in the nasopharynx and, in consequence, in the middle ear. Patients in whom rubber tubes were inserted between the gauze layers of the anterior nasal packs suffered no such inconvenience and showed no such gradients. Our work proves the value of using these tubes for pressure equalization when nasal packs are necessary.

KEY WORDS — nasal packing, pressure equalization tubes, Toynbee phenomenon, ventilation tubes.

INTRODUCTION

In an otolaryngology practice, nasal packing is a common procedure that generally follows trauma, nasal surgery, or epistaxis. Unno et al,[1] Cassisi et al,[2] and Hady et al[3] have shown that, besides the local effect of nasal packing, there are also systemic effects, such as hypoxia and hypercapnia caused by hypoventilation.

McCurdy[4] has shown recordings of negative pressure of up to -100 mm H_2O in 25% of 99 ears examined 3 days after applying bilateral nasal packing. Unilateral anterior packing produced no significant changes in middle ear ventilation. Several different pathogenic possibilities were implicated, such as lymphatic edema and venous engorgement in the nasopharynx and eustachian tube region, insufficient swallowing, and insufficient airflow through the nasopharynx. Surprisingly, few comments have been made about the severe discomfort these patients suffer.

Stucker and Ansel[5] stated that routine nasal packing is not always necessary, and in our practice we agree. However, this procedure remains the most common one for epistaxis and following nasal surgery. Stucker and Ansel also stated that the most consistent complaint from patients undergoing secondary rhinoplasty was their discomfort with nasal packs at their first procedure, turning every swallowing motion into a Toynbee maneuver, causing an annoying ear pressure sensation. The pressure changes in the nasopharynx and in consequence in the middle ear during swallowing with the nose closed have been discussed[6,7] since the pioneer work of Toynbee in 1853.[8] This phenomenon consists of a sense of fullness in one or both ears when swallowing with an obstructed nose and, as Ingelstedt and Örtegren[9] have recorded, pressure variations in the nasopharynx ranging from $+140$ to -280 mm H_2O. Most authors report that the physiologic range of pressure difference between the middle ear and the nasopharynx for air passage through the normal eustachian tube during swallowing should be above $+70$ or below -70 mm H_2O. Perlman[7] has shown that an increase in middle ear pressure of 3 to 5 mm Hg (40 to 65 mm H_2O) results in a subjective feeling of fullness.[10]

In patients with bilateral anterior nasal packing, every act of swallowing is actually a Toynbee maneuver resulting in an annoying sensation of fullness, pressure, and even pain in both ears. The act of swallowing is performed once per minute in the sleeping adult and five times per minute in the awake adult. In order to equalize the pressure in the nasopharynx in these patients, and to allow them even to breathe a little, we inserted tubes of soft rubber measuring 6 mm in their outer diameter between the antibiotic-impregnated gauze layers of the pack (Fig 1). In order to test the value of this method, we measured the gradients of pressure in the middle ear and nasopharynx in patients with bilateral anterior nasal packing and pressure-equalization tubes.

METHOD

Semirigid Nelaton No. 16 catheters were used as pressure-equalization tubes in our study. The tubes were obliquely cut and their length adjusted proportionally by first inserting them until they touched the posterior nasopharyngeal wall and then cutting their edges 3 mm short. The following measurements were taken from each patient: 1) tympanometry, 2) tympanometry after multiple swallows of water with open pressure-equalization tubes, 3) tympanometry after multiple swallows of water with closed pres-

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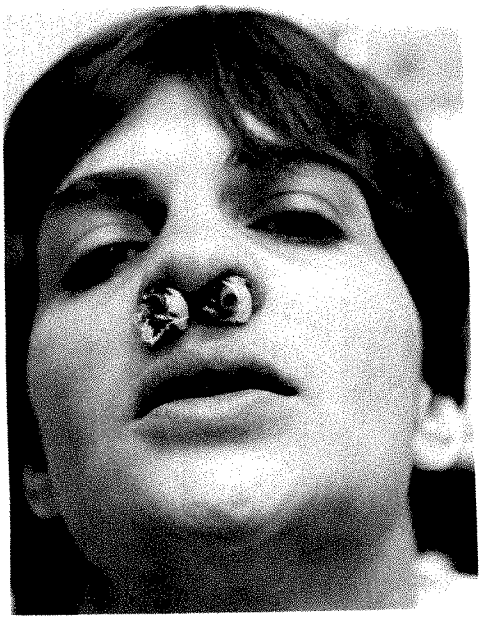

Fig 1. Anterior nasal packing combined with inserted pressure-equalization tubes.

sure-equalization tubes, 4) manometric determination of pressure changes within the nasopharynx during swallowing through one pressure-equalization tube while the other tube was open, and 5) manometric determination of pressure changes within the nasopharynx during swallowing while both tubes were closed, one by the probe of the manometer and the second by a clamp (Fig 2).

A Grason-Stadler 1723 middle ear analyzer was used to obtain tympanometric patterns and recordings of pressure changes within the nasopharynx. The analyzer used for testing eustachian tube function in patients with perforated eardrums was transformed into a pressure transducer. The probe was applied to the funnel connector of the catheter. The patient was in a sitting position and would drink water through an elastic tube to prevent unnecessary movements.

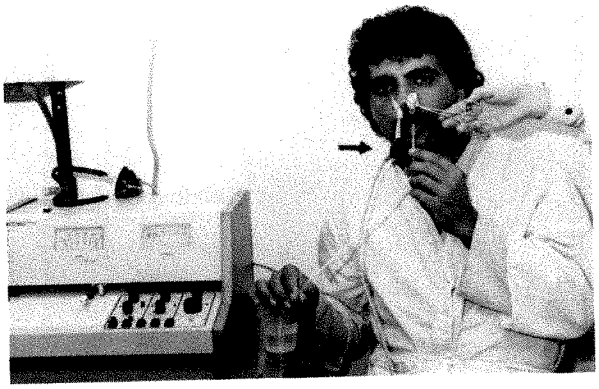

Fig 2. Manometric determination of pressure changes within nasopharynx during swallowing while both tubes are closed, one by probe of manometer (arrow) and other by clamp.

In the recordings of pressure variations, the horizontal axis represents time: 5 mm/s, and the vertical axis represents pressure: 7.5 mm/100 mm H_2O. Overpressure is recorded as upward curves and negative pressure as downward curves. Before the study, the calibration of the system was tested by a water manometer within pressure ranges of −400 to +450 mm H_2O.

Fifteen patients with bilateral anterior nasal packing after nasal septal surgery were assessed (30 ears). The ages of the patients ranged from 17 to 72 years. None had otologic disease or preoperative pathologic tympanometry. Measurements were taken daily from the first day after surgery until the packs were removed on the third day.

RESULTS

The patients in whom pressure-equalization

MEASUREMENTS OF PRESSURE GRADIENTS IN MIDDLE EAR AND NASOPHARYNX

			Nasopharyngeal Pressure Gradient During Toynbee Maneuver (mm H_2O)		*Pressure Difference After Toynbee Maneuver (mm H_2O)*		*Toynbee Maneuver Associated With Sensation of Fullness*
	Sex	*Age*	*With Closed Catheters*	*With One Catheter Open*	*Right Ear*	*Left Ear*	
1	M	45	+ 210 → − 190	0 → + 100	− 150/ + 35	+ 50/ − 100	Yes
2	M	24	+ 200 → − 100	0 → + 80	− 50/ + 25	No change	Yes
3	M	23	+ 180 → − 130	+ 130 → − 20	No change	0/ + 130	Yes
4	M	37	+ 190 → − 160	+ 10 → − 20	0/ + 100	0/ + 75	Yes
5	M	30	+ 90 → − 300	+ 100 → − 110	− 120/ + 40	− 150/ 0	Yes
6	F	33	+ 60 → − 200	0 → − 50	0/ + 40	No change	No
7	M	18	+ 150 → − 109	+ 40 → − 40	− 75/ + 75	− 50/ + 50	Yes
8	F	28	+ 150 → − 300	0 → + 130	− 90/ + 10	− 100/ 0	Yes
9	M	17	+ 260 → − 40	0 → + 20	0/ + 100	0/ + 100	Yes
10	M	67	+ 200 → − 130	+ 20 → − 40	− 30/ + 80	− 10/ − 60	No
11	M	72	+ 60 → − 140	+ 10 → − 20	No change	No change	No
12	M	33	+ 300 → − 120	+ 20 → − 50	0/ + 130	− 130/ + 30	Yes
13	M	73	+ 100 → − 230	+ 60 → − 40	− 200/ 0	− 100/ 0	Yes
14	M	60	+ 120 → − 200	+ 10 → − 40	No change	− 75/ + 30	Yes
15	F	57	+ 350 → − 160	+ 120 → − 90	0/ + 50	0/ + 200	Yes

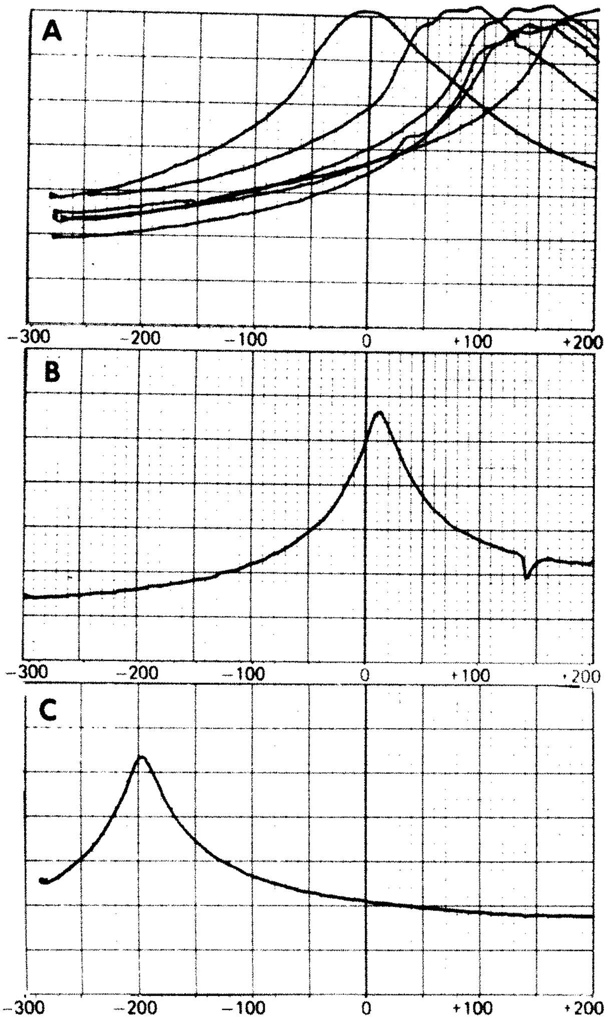

Fig 3. Tympanograms before and after multiple swallows of water with closed pressure-equalization tubes. A) Patient 15; B,C) patient 13.

tubes were used felt comfortable and had no sensation of fullness in their ears. Repeated examinations of the ears and the tympanometric measurements did not reveal a significant change in the middle ear pressure in any of the patients. In some patients the tubes tended to be blocked by plugs of bloody or thick mucous discharge. The tubes were reopened by insufflating compressed air or oxygen inside the tubes.

The results are shown in the Table. After multiple swallows of water with open tubes, none of the patients complained of fullness in the ears and the tympanograms were within normal range.

After swallowing water with the tubes closed, 12 patients (80%) complained of fullness and even pain in their ears. The immediate tympanometric measurements revealed pressure variations in the middle ear ranging from + 200 mm H_2O (patient 15, Fig 3A) to − 200 mm H_2O (patient 13; Fig 3B,C). In other patients the sensation of fullness was the result of sharp gradients of alternate positive and negative pressures in the middle ear, as in patients 1 and 7. Three patients (20%) did not complain about fullness, but stressed that they swallowed much more comfortably with open tubes. The immediate tympanometric measurements revealed no change of pressure in three ears (patient 11 and patient 6, left ear), and a pressure gradient of only 40 mm H_2O in one ear (patient 6, right ear) and of 50 mm H_2O in two ears (patient 10, both ears). During swallowing, manometric determinations through one pressure-equalization tube, while the other tube remained open, revealed pressures within the nasopharynx ranging from + 130 mm H_2O (patient 3, Fig 4A) to − 110 mm H_2O (patient 5, Fig 4B).

On the other hand, manometric measurements during swallowing with both tubes closed revealed pressure ranges within the nasopharynx from − 300 mm H_2O (patient 8, Fig 4C) up to + 350 mm H_2O (patient 15, Fig 4D). In individual subjects the pressure difference varied from 200 mm H_2O (patient 11) to 420 and 510 mm H_2O (patients 12 and 15). No complications were seen with the use of the tubes.

DISCUSSION

In the present study, very high pressure gradients in the nasopharynx were obtained, surprisingly, during the Toynbee maneuver. In previous studies,[6,7,9] pressure variations in the nasopharynx were recorded ranging from no more than + 140 to − 280 mm H_2O. We took our measurements directly from the nasopharynx, and not from the nasal cavity as other authors have done.

If the eustachian tube opens during the Toynbee maneuver, the middle ear pressure will change, depending upon the timing of the tubal opening and the pressure gradient in the nasopharynx.[11] This opening may alternately occur in the positive and the negative phase of the pressure curve in the nasopharynx.[9] For the pressure recordings of the middle ear we used tympanometry, which is an indirect method, recording only the final results of the complex series of movements of the eardrum that occur during the same single maneuver.

Using a direct method for recording tubal air passage, Ingelstedt and Örtegren[9] have shown that in several cases the middle ear cavity was insufflated and exsufflated with the same volume of air during one single Toynbee maneuver. This fact can explain why, during the tests, patients complained about annoying fullness in the ears that disappeared or became milder before the tympanograms were obtained. The repeated tympanometric measurements detected the pressure changes in the middle ear before equalization.

We conclude from the measurements of the pressure gradients in the nasopharynx that when both tubes are open, they are open enough to eliminate any significant pressure fluctuation during swal-

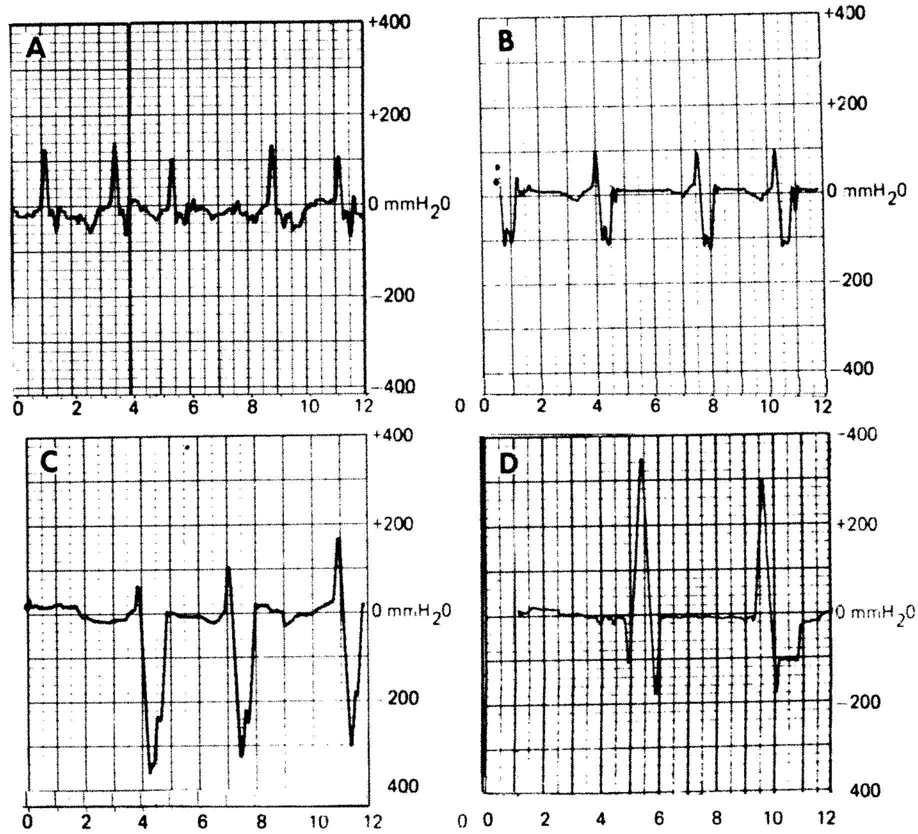

Fig 4. Pressure changes within nasopharynx during swallowing. Shown while one tube is open are A) patient 3 and B) patient 5; while both tubes are closed C) patient 8 and D) patient 15.

lowing. In patients with bilateral anterior nasal packing combined with the inserted pressure-equalization tubes, normal tympanograms were obtained. From our study we conclude that the Toynbee phenomenon provides the physiologic explanation of the negative pressure found by McCurdy[4] and by Bonding and Tos.[12] Lymphatic edema and venous engorgement in the nasopharynx and eustachian tube region, which were suggested by others, seem to us to have minor, if any, influence in producing the middle ear negative pressure in patients with bilateral anterior nasal packing.

Wallace[13] advocated the use of catheters in combination with nasal packs to allow normal nasal respiration. Wallace remarked that this technique was first described by Paulus Aegineta in the seventh century as a method in which the quills of goose feathers were inserted in the rags used as nasal packs.

The present study reveals high gradients of pressure within the nasopharynx and the middle ear that appear during swallowing in patients with bilateral anterior nasal packing. A shortcoming of the nasal packing is the discomfort of the patient, which induces fewer swallowing motions and, in certain cases, develops negative middle ear pressure. Whenever nasal packs are to be inserted, pressure-equalization tubes should be added.

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COCHLEAR HAIR CELL LOSS IN EARS WITH CHOLESTEATOMAS

SCANNING ELECTRON MICROSCOPY STUDY

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Cochleas from 16 Mongolian gerbils with spontaneous aural cholesteatomas, and four of similar age without cholesteatomas, were examined by scanning electron microscopy to quantify cochlear hair cell loss. Loss of hair cell stereocilia was found in all ears with cholesteatomas and was significantly increased when compared with uninvolved ears from animals of similar age. The hair cell loss associated with gerbilline cholesteatomas appeared to be most marked in the middle turn of the cochlea and increased in severity with increasing size of the cholesteatomas. Outer hair cells were affected more than inner hair cells. Inner and outer hair cell loss was not significantly different in infected cholesteatomas versus sterile cholesteatomas. The greater damage to hair cells at the middle turn compared to the basal turn suggests that these losses may be the result of some agent acting through the cochlear wall rather than through the round window.

KEY WORDS — cholesteatoma, hair cells, scanning electron microscopy.

INTRODUCTION

Aging Mongolian gerbils (*Meriones unguiculatus*) spontaneously develop aural cholesteatomas.[1] In some animals, the presence of cholesteatomas is associated with auditory deficits that are greater than would be expected from conductive hearing losses alone,[2] and it is likely that such animals sustain sensorineural deficits. Studies of humans with chronic otitis media, with or without cholesteatomas, have shown sensorineural losses,[3] presumably due to hair cell injury. Gerbils with advanced stages of cholesteatomas of long duration usually have an associated chronic otitis media; pathogenic bacteria have been cultured from the cholesteatomas and the middle ears of such animals.[4] Several mechanisms for hair cell damage are possible in this animal model:

1. Chronic otitis media may lead to inner ear damage through the round or oval window or through the cochlear wall[4]; or
2. Direct erosion of the bone overlying the cochlea may lead to inner ear infection and hair cell damage; or
3. The presence of cholesteatomas alone, without bone erosion or infection, may lead to cochlear hair cell loss by other mechanisms.

The purpose of this study was to determine if gerbils with cholesteatomas have cochlear hair cell loss, and if the hair cell loss is related to the stage and invasiveness of the cholesteatoma[1] or to the presence of pathogenic bacteria in the middle ear.[4]

METHODS AND MATERIALS

Twenty Mongolian gerbils, *Meriones unguiculatus*, reared in our colony, were used for this study. The animals were first and second generation progeny of breeding stock obtained from Tumblebrook Farms and were raised under quiet conditions. The animals used in this study included 16 of the 29 gerbils used in a study of the bacterial flora of gerbilline cholesteatomas.[4] Therefore, the bacteria present in the middle ear and cholesteatoma were known for each animal. Animals were over 1 year of age. Four animals of comparable age without cholesteatomas were used as controls. Each animal was killed by intraperitoneal injection of pentobarbital, and its bullae were dissected.

The stage[1] of each cholesteatoma was determined: stage I, keratin accumulation on tympanic membrane only; stage II, cholesteatoma protruding into middle ear but not contacting the cochlear wall; stage III, cholesteatoma contacting the cochlear wall; stage IV, cholesteatoma filling the bulla; stage V, cholesteatoma with intracranial invasion.

After we obtained specimens for a microbiology study,[4] the cochleas were perfused by gently injecting 2% paraformaldehyde, 2% glutaraldehyde in 0.08 *M* cacodylate buffer at 4°C into the oval window until fixative flowed out a small opening made at the apex of the cochlea. Fixative was infused within 1 minute after the removal of the bulla. After fixation for 1 hour, the cochleas were washed with buffer and postfixed with 1% OsO_4 for 1 hour at 4°C. The cochleas were dissected under buffer solution by use of a binocular dissecting microscope. While stabilizing the cochlea and adjacent bone with toothed forceps, we made small fractures in the bony wall of the cochlea with a sharp pick. The dissection was facilitated by immersing the cochlea in clean buffer solution; a gentle stream of liquid was used to flush away bone chips. Larger bone chips were removed with fine forceps. After removal of the lateral bony wall, the spiral ligament and the stria vascularis were removed with

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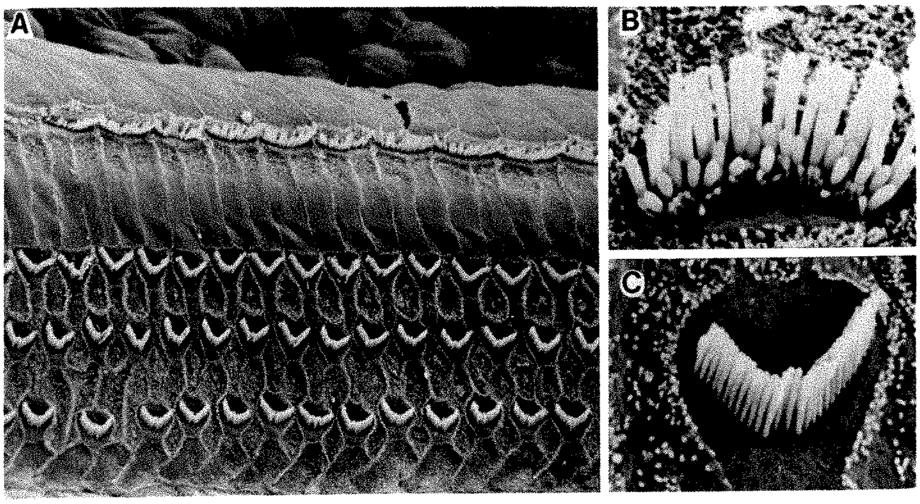

Fig 1. Scanning electron micrographs of middle turn of normal gerbil cochlea. A) Low power view shows normal relationship of inner and outer hair cells (original x700). B,C) Higher power views of inner (B) and outer (C) hair cell apices show uniform orientation of stereocilia (original x3,500). Surrounding Deiters' cells have microvilli.

sharpened forceps, leaving the organ of Corti in place.

After dissection, specimens were washed in distilled water and placed in a saturated solution of thiocarbohydrazide (TCH) for 30 minutes. After another washing, the specimens were placed into 1% OsO_4 for 2 hours; then the TCH and osmium steps were repeated twice: the OTOTO method.[5] The specimens were washed in distilled water, dehydrated in graded solutions of acetone, and critical point dried. The mounted specimens were screened on an ISI-DS130 scanning electron microscope at a magnification of 700, and each available region of the organ of Corti was photographed.

Hair cell counts were derived by counting the presence or absence of each inner and outer hair cell. A cell was counted as missing if there were no identifiable stereocilia on the surface. The percentage of hair cells remaining in each of 11 areas of equal size along the basilar membrane was determined, and a cytocochleogram was made. In each group, derived cytocochleograms were obtained from several cochleas. Sometimes sections of the organ of Corti were missing from a given specimen and were discounted for the purpose of deriving the averaged cytocochleogram.

For the purposes of statistical analysis, each cochlea was divided into three sections: apical, middle, and basal. The 11 equal segments used for the cytocochleograms were designated as follows: segments 1 to 3 as apical, segments 4 to 7 as middle, and segments 8 to 11 as basal. Comparisons between groups were performed using a two-way analysis of variance (ANOVA).[6]

RESULTS

Gerbils with spontaneous cholesteatomas lost cochlear hair cells, with the outer hair cells more affected than the inner hair cells. Generally, outer hair cell loss was greater in the middle turn of the cochlea than at the apex or the base. Loss of inner hair cells was seen only when severe outer hair cell loss had occurred.

When contrasted to the normal organ of Corti (Fig 1), the affected areas showed loss of stereocilia of the outer hair cells (Fig 2). The third row of outer hair cells generally was affected before the first and second rows. The earliest changes in the outer hair cells were loss of the regular structure of the stereocilia, bending of cilia, and fusion of adjacent cilia (Fig 2). The inner hair cells appeared to be damaged only with severe outer hair cell loss (Fig 3).

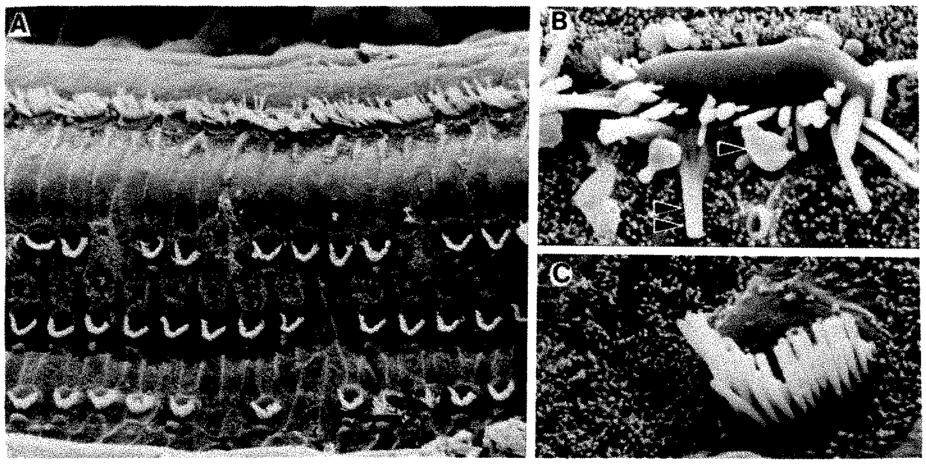

Fig 2. Scanning electron micrographs of middle turn of gerbil cochlea with cholesteatoma that had moderate amount of damage. A) Outer hair cells are affected more than inner hair cells (original x700). B) Damaged inner hair cells have disarrayed and fused stereocilia (double arrowhead) and blebs on stereocilia remnants (single arrowhead) (original x3,500). C) Outer hair cell damage appears as total loss of cilia and replacement of cells by phalangeal scars (original x3,500). Remaining hair cells appear to have normal stereocilia.

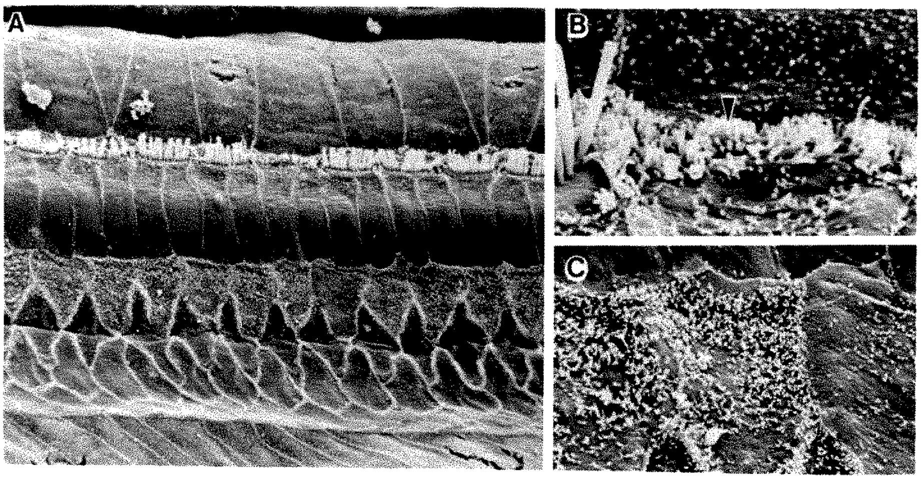

Fig 3. Scanning electron micrographs of cochleas with most extensive hair cell loss associated with cholesteatomas. A,C) Outer hair cells were sometimes completely absent and replaced by phalangeal scars. A) Original x700, and C) original x3,500. B) In most extreme cases inner hair cell loss was also seen. Increased number of microvilli (arrowhead) were seen in region of missing inner hair cells (original x700).

The inner hair cells were noted to be larger in their basal-apical diameter than were the outer hair cells. Thus, for every ten outer cells in a given row, seven adjacent inner hair cells were counted.

In the control animals without cholesteatomas, there were some losses of inner and outer hair cells throughout the cochlea. Some outer hair cell loss was seen without loss of inner hair cells (Fig 4A).

In the apical turn, outer hair cell loss increased as a function of increasing stage of the cholesteatoma ($F_{4,30} = 19.6$, $p < .0001$), but there was no correlation of stage and inner hair cell loss ($F_{4,30} = 1.19$, p = NS). Similarly, in the basal turn, outer hair cell loss increased with increasing stage ($F_{4,30} = 6.62$, $p = .0008$), and there was no significant effect upon inner hair cells ($F_{4,30} = 1.26$, p = NS). In the middle turn, however, while there was also an effect of increasing stage upon inner hair cell loss ($F_{4,30} = 2.85$, $p = .040$), the effect of stage on outer hair cell loss was strong ($F_{4,30} = 6.92$, $p = .0007$) in the middle turn.

In ears with stage II cholesteatomas, loss of outer hair cells was greater only in the apex (Fig 4B) than in ears without cholesteatomas (apical: $F_{1,15} = 10.55$, $p = .0005$; middle: $F_{1,15} = 4.36$, $p = .052$; basal: $F_{1,15} = 3.84$, $p = .056$). When cochleas were examined from ears with large cholesteatomas (stages III, IV, or V), the loss of hair cells, especially outer hair cells, was seen in all turns (for all comparisons $p \leq .021$; Fig 4C-E). Outer hair cell loss appeared most marked in the middle turns of the cochleas associated with stage III, IV, and V cholesteatomas (those contacting the bone of the cochlea and the bulla wall).

When the average cytocochleograms from animals with infected cholesteatomas (n = 11; Fig 4F) were compared with sterile cholesteatomas (n = 5; Fig 4G), there was no significant effect on inner hair cells (apical: $F_{1,28} = 0.16$, p = NS; middle: $F_{1,28} = 3.13$, p = NS; basal: $F_{1,28} = 0.50$, p = NS) or on outer hair cells (apical: $F_{1,28} = 0.88$, p = NS; middle: $F_{1,28} = 3.14$, p = NS; basal: $F_{1,28} = 3.40$, p = NS).

DISCUSSION

Loss of hearing and of cochlear hair cells has been observed in both animals[7,8] and humans[4] with otitis media. Experimental effects of otitis on hair cells have been equivocal. Hodges et al[7] found only scattered loss of outer and inner hair cells in rats with experimentally induced otitis media due to *Streptococcus pneumoniae*, but they noted extensive hair cell loss in two ears with severe spontaneous otitis media. They observed a sequence of hair cell injury similar to that seen in the animals in the present study. The earliest changes were disorientation and fusion of stereocilia; loss of outer hair cells occurred before loss of inner hair cells. Penny et al[9] recently showed fewer changes in hair cells in rats with *Hemophilus influenzae*-induced otitis media than in a previous study with *S pneumoniae.*[7] In these two studies, cracks were observed in the Deiters' cells between the cuticular surfaces of the outer hair cells. We did not observe similar cracks and concavities in this study, but the differences may be explained by a difference in technique; in the studies by Hodges et al[7] and Penny et al,[9] specimens were critical point dried after fixation and then sputter-coated; in this study, the cochleas were fixed by the OTOTO method without coating.[5]

In this study, infected cholesteatomas were not associated with more cochlear hair cell loss than those without pathogenic bacteria. The hypothesis that cochlear hair cell loss occurs as a result of chronic infection alone[3] should be reexamined in the light of these findings. The effect of chronic infection on cochlear hair cells is unknown.

There was more hair cell loss associated with larger, more advanced cholesteatomas. The larger cholesteatomas generally have more destruction of cochlear bone. Thus, bone resorption may be a causal factor in hair cell loss. Similarly, large cholesteatomas probably have been present for a longer

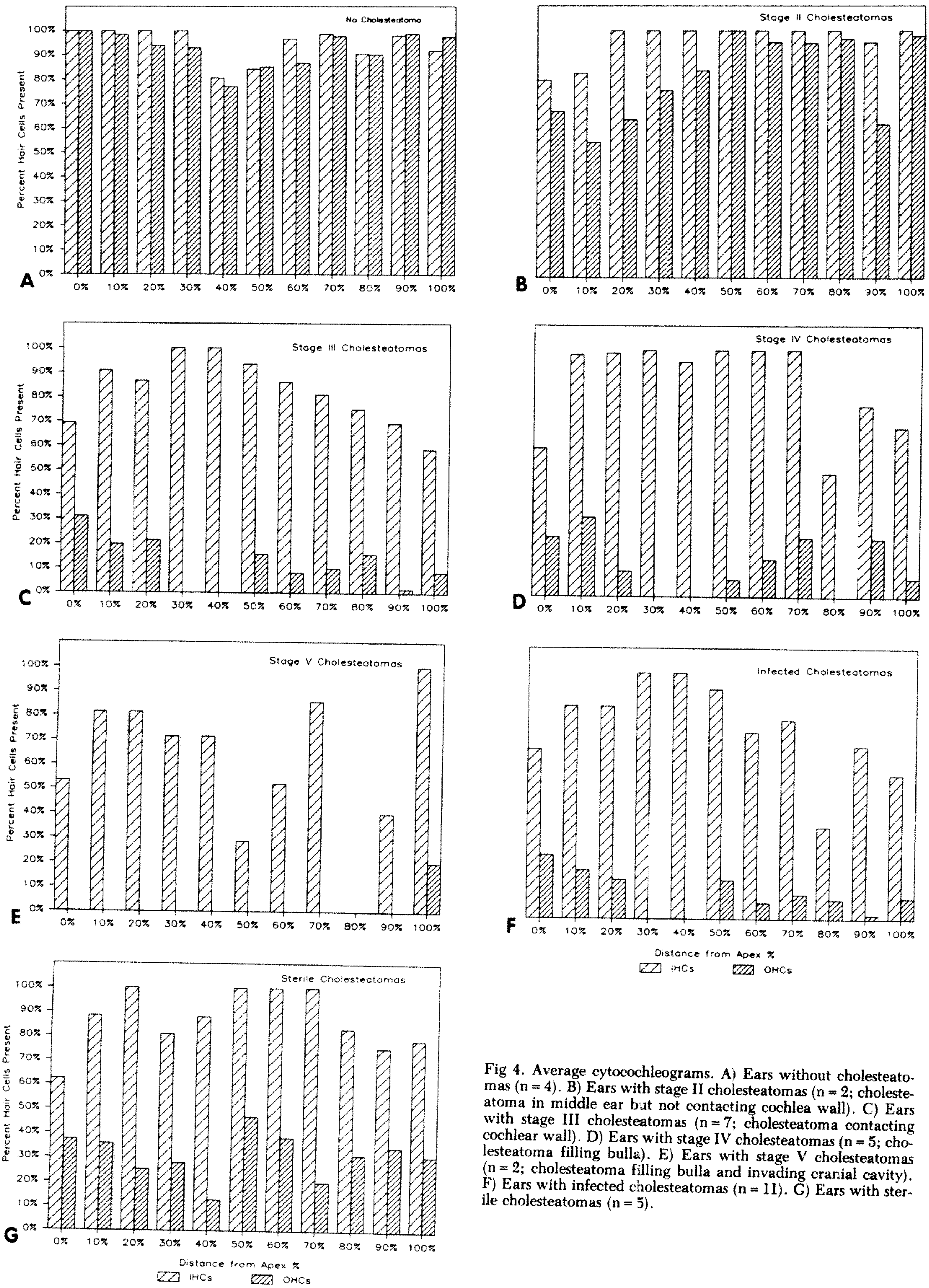

Fig 4. Average cytocochleograms. A) Ears without cholesteatomas (n = 4). B) Ears with stage II cholesteatomas (n = 2; cholesteatoma in middle ear but not contacting cochlea wall). C) Ears with stage III cholesteatomas (n = 7; cholesteatoma contacting cochlear wall). D) Ears with stage IV cholesteatomas (n = 5; cholesteatoma filling bulla). E) Ears with stage V cholesteatomas (n = 2; cholesteatoma filling bulla and invading cranial cavity). F) Ears with infected cholesteatomas (n = 11). G) Ears with sterile cholesteatomas (n = 5).

period of time, increasing the time of exposure to the causal agent.

The outer hair cells of the middle turn of the cochleas appeared to be more damaged than those of the apical or basal turns. The only statistically significant effect of stage on inner hair cells was in the middle turn (p = .040). If hair cell loss were due to infection and passage of toxic substances through the round window, one would expect a greater effect on the hair cells of the basal turn. Gerbilline cholesteatomas contact the bone of the middle cochlear turn prior to contact with other portions of the cochlea. These findings suggest two possible explanations:

1. The damage is due to a toxin from the middle ear that crosses the round window, and there is greater hair cell loss in the middle turn because these cells are more susceptible to damage; or
2. Hair cells of the middle turn are damaged by direct effects through the bony wall of the cochlea.

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SPINAL ACCESSORY NERVE FUNCTION FOLLOWING NECK DISSECTION

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Spinal accessory nerve (SAN) function was evaluated by electromyography (EMG) and muscle testing in 36 patients who underwent neck dissection with SAN preservation. The results emphasized that SAN function was relatively good after conservative neck surgery. Muscle testing findings showed better function than did EMG findings. After surgery the trapezius muscle functioned more efficiently than the sternocleidomastoid (SCM) muscle probably because of the more traumatic surgical handling of both the SCM muscle and its SAN branch. In order to obtain the functional advantages of SAN preservation, the authors suggest that the conservative procedure in radical neck dissection be used whenever warranted by oncologic diagnosis.

KEY WORDS — accessory nerve, electromyography, head and neck neoplasms, neck surgery.

INTRODUCTION

The functional neck dissection first described by Suarez[1] in 1963 and further modified by Bocca[2] in 1966 requires the removal of lateral cervical lymph-bearing tissue while preserving important structures of the neck, such as the internal jugular vein, the spinal accessory nerve (SAN), and the sternocleidomastoid (SCM) muscle.[3-6]

The SAN is entirely motor in function and innervates two important muscles: 1) the SCM muscle, supplied by a few fibers from the second and third cervical nerves, and 2) the upper portion of the trapezius, the lower part of which is supplied by the third and fourth cervical nerves.

The shoulder syndrome[7] due to SAN transection is the most frequent complication following radical neck dissection. This syndrome is characterized by pain in the involved shoulder joint, limitation in the abduction movements with full passive range of movement, electromyographic (EMG) abnormalities, and anatomic deformities. The affected shoulder droops and shows forward and downward displacement of the scapula, of which the vertebral border becomes flared. To avoid this syndrome, many surgeons try to conserve the SAN in classic radical neck dissection.[8-13]

The purpose of this study was to evaluate the function of the SAN by means of EMG and the strength of the SCM and trapezius muscles in patients who have undergone neck dissection with SAN preservation.

MATERIALS AND METHODS

The function of the SAN was evaluated by examining the trapezius and SCM muscles in a random group of 36 of 167 patients treated in our hospital with monolateral or bilateral neck dissection for malignancies in the period 1975 to 1985. Of these 36 patients, 26 underwent monolateral functional neck dissection, two had atypical monolateral radical neck dissection (with SAN preservation), seven had bilateral functional dissection, and one had atypical radical dissection and contralateral functional dissection. The total number of neck dissections was 44 (41 functional and three atypical radical). In all we investigated 44 trapezius and 41 SCM muscles.

The mean patient age was 57.8 years, ranging from 37 to 75 years. There was an absolute predominance of men (only one was a woman). Follow-up ranged from 1 month to 10 years 8 months, with the average being 3½ years.

There were two control groups, one consisting of ten healthy subjects and the other including ten patients who had undergone classic radical neck dissection with SAN transection. The same methods, muscle testing (MT) and EMG, were used to study each of the three groups. Testing for the trapezius muscle was performed by holding the examiner's hands against the patient's achromial region and asking the patient to raise the shoulder as strongly as possible against resistance. The SCM muscle was investigated by holding the examiner's hand against the homolateral side of the patient's chin and asking the patient to rotate the head against resistance as strongly as possible. Then the examiner rated the patient's strength from 0 (absence of movement) to 5 (full strength) according to the standard of Daniels et al.[14]

Electromyographic tests were performed on the trapezius and SCM muscles using an MK 3 Medelec

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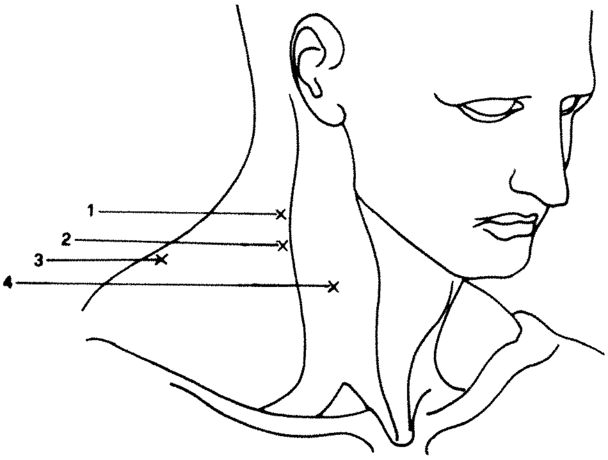

Electromyographic reference points. 1 — stimulating electrode, 2 — Erb's point, 3 — recording needle electrode for trapezius muscle, 4 — recording needle electrode for SCM muscle.

electromyograph with a sound transducer (loudspeaker), a visual transducer (cathode-ray oscilloscope), and a light-sensitive paper recording unit. We used Adrian-Bronx coaxial needle recording electrodes. The stimulating electrode consisted of two metal plates set on an insulating support. The indifferent electrode was a metal disk tied to the patient's wrist with a rubber strap.

Each patient was informed about the examination procedure. The patient sat on a chair with the forearm lying on the thighs and inert. During the trapezius muscle test, the patient kept the head straight up and was asked to look at a hypothetical point 5° to 10° above the visual horizon. When the subject was completely relaxed, the electric silence of both trapezius muscles could be reached. The recording needle electrode was inserted into the trapezius muscle at the crossing point between the hemiclavicular line and the upper edge of the muscle. The stimulating electrode was placed on the skin at Erb's point (see Figure).[15]

To test the SCM muscle, the recording needle electrode was inserted into the middle third of the muscle, whereas the stimulating electrode was placed at about 3 to 3.5 cm vertically above Erb's point (see Figure).[15] The electric silence of the SCM muscle could be reached when the patient's head was bent 30° forward and turned about 20° to 25° toward the examined SCM muscle. The ground electrode was placed on the ipsilateral wrist, but this did not entail any significant change in the recordings. The recording paper speed was 50 cm/s. The recordings were carried out at muscle rest, medium strain, and maximal strain. Stimulating impulses were square waves of 120-mV amplitude and 0.15-second duration.

We regarded as normal those motor unit action potentials that showed two, three, or four phases, with an amplitude ranging from 0.2 to 0.3 mV, and from 5 to 15 ms in duration under minimal strain or an interference pattern under maximal strain.

We defined slight neurogenic peripheral lesions as follows.

1. Fibrillation signs at rest, sometimes including slow denervation potentials or Jaspers (spontaneous potentials lasting longer than 1.5 to 2 ms, with up to 0.1-mV amplitude and frequency ranging from 2 to 30 Hz).
2. Slight decrease of motor unit potentials' number and amplitude; reduced interference pattern under maximal strain.
3. Remarkable increase of motor unit potentials' average duration.

We defined severe neurogenic peripheral lesions as follows.

1. Fibrillation and Jaspers at rest.
2. Remarkable decrease of motor unit potentials' number and amplitude; under maximal strain the recording did not show an interference pattern but remained at an intermediate stage (it ranged from discrete activity to a single fiber potential's shape).
3. Increase of motor unit potentials' discharge rate (40/s in normal subjects, 60/s or more in pathologic cases).
4. Increase of polyphasic forms (3% to 12% in normal subjects) probably due to peripheral branching of the regenerating nerve fibers.

RESULTS

As expected, all the subjects of the healthy control group had normal EMG and MT results for both trapezius and SCM muscles.

All the patients of the classic radical neck dissection group had severe neurogenic peripheral lesions of the trapezius muscle with shoulder pain and severe muscle weakness.

Trapezius muscle EMG findings are shown in Table 1. The six patients who underwent functional neck dissection resulting in a slight neurogenic peripheral lesion were examined 1 month, 3 months, 7 months, 2 years 2 months, 10 years 6 months, and 10 years 8 months after surgery. In one of these patients we found muscle fibrillation. The patient who had a severe neurogenic peripheral lesion was examined 2 years 2 months after surgery.

Muscle testing data from the 44 trapezius muscles are shown in Table 1. The patient with remarkable shoulder weakness (score of 2) also showed a severe neurogenic peripheral lesion on EMG.

Table 2 shows EMG and MT findings of the SCM muscles. (Obviously no comparison with radical neck dissection is possible.) The very high rate of normal MT results (95%) is remarkable. Less favorable results were found on EMG, with about a 50% rate of slight neurogenic peripheral lesions.

TABLE 1. TRAPEZIUS MUSCLE DATA

	Healthy Subjects	*Classic Radical Neck Dissection Group*	*Conservative Neck Dissection Group*
Electromyography			
Normal	10 (100%)	0	37 (84.1%)
Slight peripheral neurogenic lesions	0	0	6 (13.6%)
Severe peripheral neurogenic lesions	0	10 (100%)	1 (2.3%)
Total	10	10	44
Muscle testing			
Strength 5	10 (100%)	0	39 (88.6%)
Strength 4	0	0	4 (9.1%)
Strength 3	0	0	0
Strength 2	0	4 (40%)	1 (2.3%)
Strength 1	0	6 (60%)	0
Strength 0	0	0	0
Total	10	10	44

TABLE 2. STERNOCLEIDOMASTOID MUSCLE DATA

	Healthy Subjects	*Conservative Neck Dissection Group*
Electromyography		
Normal	10 (100%)	21 (51.2%)
Slight peripheral neurogenic lesions	0	20 (48.8%)
Severe peripheral neurogenic lesions	0	0
Total	10	41
Muscle testing		
Strength 5	10 (100%)	39 (95.1%)
Strength 4	0	2 (4.9%)
Strength 3	0	0
Strength 2	0	0
Strength 1	0	0
Strength 0	0	0
Total	10	41

DISCUSSION

It has long been known that patients treated with classic radical neck dissection with complete SAN transection show the shoulder syndrome.[16] Patients treated with rehabilitative therapy based on active movements sometimes show less serious troubles.[17,18] In agreement with Valtonen and Lilius[18] and Carenfelt and Eliasson,[16] we think that "a SAN injury is a serious, invaliding complication," and we can observe that these patients feel handicapped in their daily occupations because of this lesion.

Bagatella et al[19] reported that 17 patients who had undergone functional neck dissection were affected by SAN electric inexcitability and trapezius denervation with muscular trophism disorders, functional deficiency, and pain 3 months after functional neck dissection. Six months after surgery, the SANs of 15 of 17 patients had increased electric excitability with a better muscular trophism. After 12 months, the 15 patients had quite normal EMGs; only a third of them completely recovered the muscular trophism. The shoulder pain persisted in 25% of the cases. The patients whose SAN function had not recovered had suffered irreversible anatomic damage on surgery.

Examining 17 SCM muscles of patients who had undergone monolateral functional neck dissection, Fiorella et al[20] found EMG abnormalities of various degrees in all the muscles, but good clinical function.

Our study emphasizes more positive data. In only one case did we observe a severe neurogenic peripheral lesion with serious shoulder weakness (trapezius muscle score of 2; SCM muscle score of 4). None of the six patients with slight neurogenic peripheral lesions complained of the shoulder syndrome. Four of them showed no MT abnormalities, whereas one was affected by a slight trapezius muscle and SCM muscle strength decrease (score of 4), and the last one showed a slight trapezius muscle strength decrease (score of 4). Moreover, in three of six cases, the follow-up was 1, 3, and 7 months. Therefore, we can suppose that the SAN may regain its function. As a matter of fact, EMG normalization is generally observed 1 year after surgery. As for the other three patients, whose follow-up was 2 years 2 months, 10 years 6 months, and 10 years 8 months, the damage seems to be irreversible, and it may have been caused by traumatic surgical handling. We found a satisfactory correlation between EMG data and MT results for the trapezius muscle, and we think that MT is a good enough technique for a reliable SAN function evaluation. This correlation was not as good for the SCM muscle, because the MT results were clearly better than the EMG data. In our opinion, this must be ascribed to the synergistic action of the other neck muscles that usually cooperate with the SCM muscle in head rotation.

We found that the patients with neurogenic peripheral lesions of the SCM muscle (48.8%) outnumbered those with trapezius muscle damage (15.9%). We believe the difference is due to the small dimension of the SAN branch innervating the SCM muscle, and to the more significant surgical trauma.

Thus, functional neck dissection preserves not only the jugular vein patency, as shown by one of the authors in a previous report,[21] but also good function of the spared muscular structures. The trapezius muscle, which is more important than the SCM muscle in shoulder muscular dynamics, completely recovers its function after conservative surgery, as shown by EMG and MT data. The SCM muscle seems less efficient on EMG examination, even though it fully regains its function.

Considering the oncologic value of this surgical technique, confirmed by many authors, we believe that if the surgeon is careful in handling the SAN trunk, the spared structures can easily regain their function. Just after surgery both clinical and EMG signs of neurapraxia may occur, but they nearly always disappear in a few months.

We are further led to add that considerable functional advantages can be obtained in many cases of classic radical neck dissection in which it is possible to spare the SAN external branch. The patients who have undergone this atypical radical dissection do not complain of shoulder pain or deformities. Upper limb movements are well preserved, and the removal of the SCM muscle entails no disorders or, at the most, slight ones.

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STAPEDIAL ELECTROMYOGRAMS RECORDED BY ELECTROCOCHLEOGRAPHY

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The stapedial reflex (SR) can be obtained by the impedance method only when the middle ear is intact. In order to examine the function of the stapedius muscle in diseased ears, the recording of the stapedial electromyogram by an electrocochleographic (ECoG) method was considered. The SR was recorded simultaneously by the impedance method in ten normal subjects for comparison. The outputs of ECoG were averaged by a signal processor up to 200 times under a longer sweep time, and a large biphasic wave with a latency of about 11 ms was obtained on the ECoG records. The amplitude increase of the biphasic wave caused by raising the intensity of the acoustic stimulation paralleled that of the SR. This means that the biphasic wave obtained by ECoG with a latency of about 11 ms originated from the stapedius muscle.

KEY WORDS — electrocochleography, postauricular response, stapedial electromyogram, stapedial reflex.

INTRODUCTION

It is widely known that an acoustic stimulus evokes a postauricular response (PAR)[1-5] and stapedial reflex (SR).[6-13] These constitute the acoustic facial reflex. The latency and amplitude of these responses vary according to the presence of pathway lesions, such as acoustic tumors, multiple sclerosis, or facial paralysis. The latency, amplitude, and decay of the PAR and SR can be used to determine the degree of facial involvement in these diseases. As measured by the impedance method, however, the SR contains not only stapedius muscle contraction, but also eardrum-ossicular components. That is, it is not a direct measurement of stapedius muscle function induced by the acoustic facial reflex.

Since the stapedius muscle is located in the tympanic cavity, electromyograms (EMGs) of this muscle can be obtained by electrocochleography (ECoG), such as action potential (AP) and summating potential (SP), if a longer analysis time or sweep time is adopted than for AP and SP recordings. In this study, a stapedial electromyogram (SEMG) was recorded by ECoG in normal subjects and patients. In normal subjects, SRs were recorded simultaneously by the impedance method to compare both results. A patient with an acoustic tumor and one with tympanoplasty I also were examined to make sure that the waves obtained originated not from the PAR but from the stapedius muscle.

APPARATUS AND METHOD

Electrocochleography with low cut (100 Hz) and high cut (1,000 Hz) filters was used to record the SEMG (Fig 1), and the impedance method to record the SR simultaneously. The impedance audiometer was Amplaid 702. Since ordinary Amplaids could not produce acoustic stimuli by external trigger pulses, one was modified to make this possible, and also to enable the recording of SR waves that are not filtered. The outputs of SR were put into channel 2 of a signal processor (Nihon Kohden MEB-3102).

For the acoustic stimulus, the trigger pulse of a pulse generator was used at a stimulus interval of 800 ms, a stimulus duration of 50 ms with rise and fall time of about 10 ms, and a stimulus frequency of 1,000 Hz on the Amplaid 702.

A silver ball electrode was placed near the tympanic annulus as a recording electrode for SEMG. The reference electrode was placed at the earlobe, and the ground electrode near the nasion. The

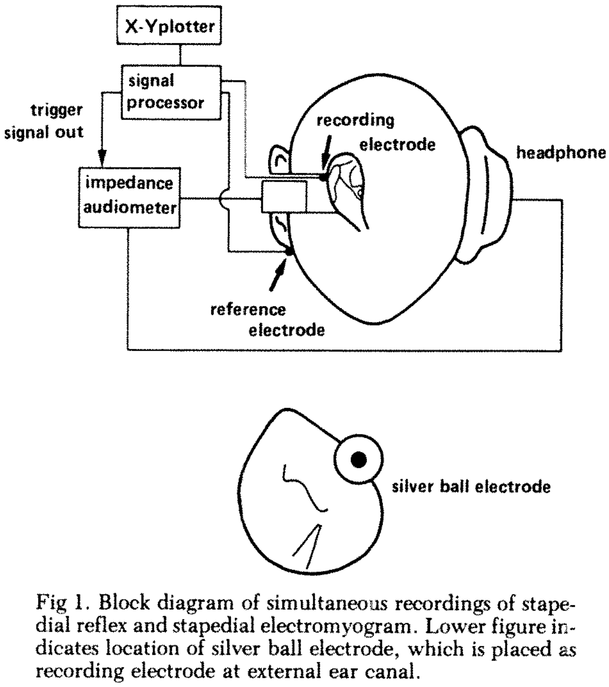

Fig 1. Block diagram of simultaneous recordings of stapedial reflex and stapedial electromyogram. Lower figure indicates location of silver ball electrode, which is placed as recording electrode at external ear canal.

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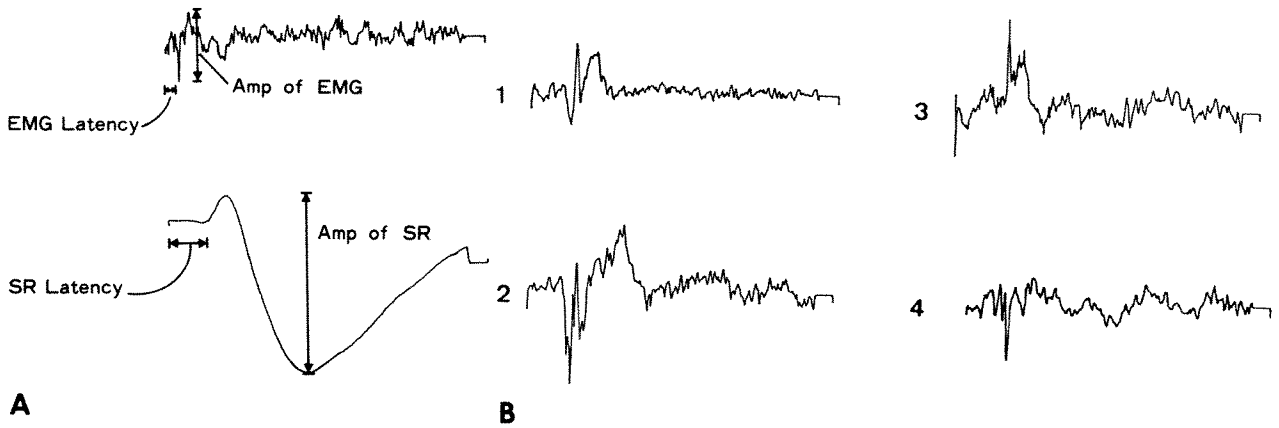

Fig 2. A) Stapedial electromyogram (EMG) and stapedial reflex (SR) recorded simultaneously, showing methods for calculation. Sweep time is 500 ms. B) Several patterns of stapedial EMGs. No. 1 was most frequent.

signals from it were put into channel 1 of the signal processor.

In normal subjects, the amplitude of SR varied in individual cases and with the levels of sound stimuli, so that all records from SRs, SEMGs, and acoustic stimuli were stored temporarily in a DATA recorder (Sony Magnescale Corp, FE-39A), reprocessed, and averaged 200 times. The waves acquired were drawn by an X-Y plotter. For SR waves, a 500-ms analysis time was adopted to observe their entire change, and for SEMGs, a 100-to 200-ms analysis time was chosen to measure the latency and form of the waves. The sound pressure levels used were 95 to 115 dB HL (contralateral stimulation) and 95 to 110 dB HL (ipsilateral stimulation), which SEMG could sense. In the following context, the expression dB in simultaneous recording means dB HL.

When SEMG waves only were recorded in the diseased ear, a sound generator (DANA Japan DA-502A) was used to produce acoustic stimuli. The conditions were as follows: frequency, 1,000 Hz; repetition rate, 800 ms; duration, 50 ms. Sound was delivered through TDH 490 earphones. Sound intensity was expressed in decibels (JIS T1201, 1963).

Subjects. Subjects for the simultaneous recording were ten healthy persons (eight men and two women) without any previous illness of the facial nerve, CNS, or ear. Recording of SEMG waves only with ECoG was done in one patient with an acoustic tumor and in one patient with a perforated eardrum after tympanoplasty I.

RESULTS

Normal Subjects. Figure 2A illustrates simultaneous recording of EMG and SR in one normal subject during 115-dB contralateral acoustic stimulation. The upper tracing is the record of averaged EMG obtained by ECoG. At about 11 ms, a biphasic wave was observed, the amplitude of which increased at every addition. The lower tracing is the SR wave. It shows clearly that the compliance of the SR decreased at the beginning and then increased gradually.

Figure 2B shows several patterns of biphasic waves of averaged EMG at a 200-ms sweep. Number 1 is the most frequent, followed by No. 2, No. 3, and No. 4, in that order. The level of EMG recording from the eardrum was so small that in some cases EMG changes could not be measured because they were buried in noise.

Figure 3A shows typical amplitude changes in SR and EMG when the sound pressure levels of stimulation of the contralateral side varied from 100 to 115 dB. Both SR and EMG amplitudes increased with the increasing intensity of the acoustic stimulus.

Figure 3B shows the correlation between EMG amplitude change and SR amplitude change when the maximum values of SR and EMG were regarded as 100%. Stapedial reflex amplitude and EMG amplitude showed a linear relation within the range of 95 to 115 dB; the correlation coefficient (γ) in this case was 0.995. The mean and SD of γ for 12 ears in cases of simultaneous recordings were 0.855 ± 0.093, a good correlation.

With contralateral stimulation, the latency of SR changed with the intensity of the stimulation, as seen in Fig 4A. As the sound intensity increased, the latency of the SR was shortened, whereas the latency of the EMG was not affected. On the other hand, EMG latency after ipsilateral stimulation was constant, and SR latency also was fairly steady.

In the following calculations, we used only those values that were obtained when both SR and EMG could be detected and recorded simultaneously at >100 dB (ipsilateral stimulation) or >105 dB (contralateral stimulation).

Figure 4B shows the distribution graphs of EMG latencies. With contralateral stimulation, the mean and SD of latencies were 10.07 ± 1.31 ms ($n = 21$), and with ipsilateral stimulation they were 11.09 ± 1.53 ms ($n = 22$). It seems that with EMG, the latency is around 11 ms with both ipsilateral and contra-

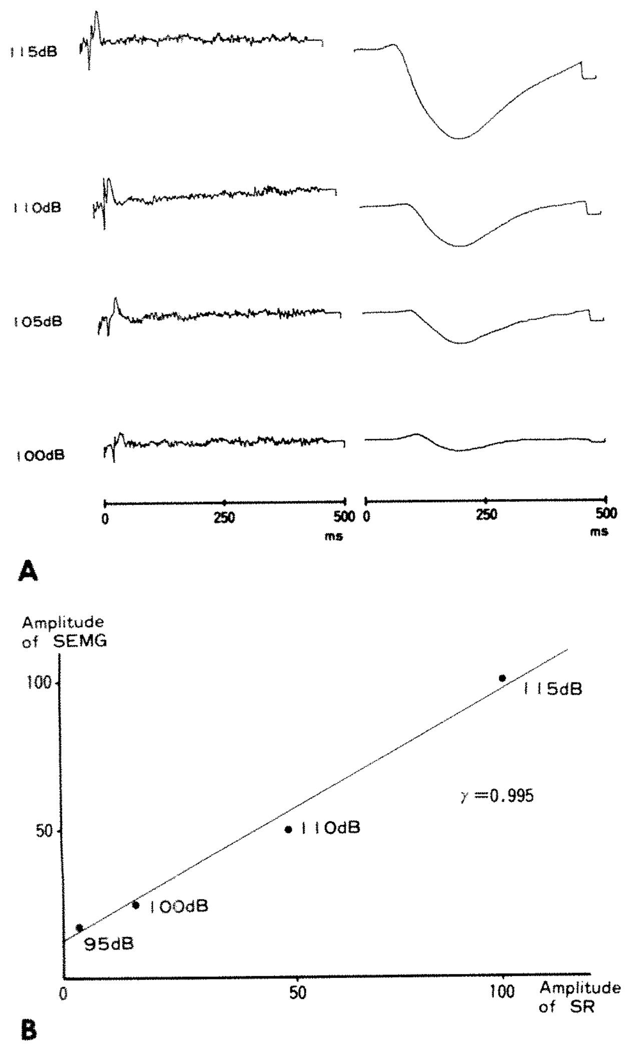

Fig 3. A) Change in amplitude of stapedial EMG (SEMG) (right) and SR (left). B) Correlation between SEMG amplitude and SR amplitude. Amplitude of biphasic waves at about 11 ms on SEMG recording increased linearly with increase of SR amplitude caused by contralateral acoustic stimulation.

lateral stimulation. The contraction of the stapedius muscle began around 11 ms after the acoustic stimulus had been delivered.

The onset of SR varied with the sound intensity. The latency was shortest at 115 dB, and prolonged as the sound pressure decreased. Figure 4C shows the distribution graphs of SR latency. As the latency of SR varied with the sound intensity changes, the mean and SD of SR latencies ranged widely: 58.00 ± 12.84 ms (n = 18) with contralateral stimulation and 36.14 ± 11.62 ms (n = 21) with ipsilateral stimulation.

Patients. Figure 5A shows the EMG changes before and after surgery for acoustic neurinoma. In the record taken before surgery (upper tracing) there was a clear biphasic wave at about 14 ms. After the surgery, however, there was complete paralysis, and even the ordinary SRs did not appear. The biphasic wave that existed before surgery could not be detected after surgery, as seen in the lower tracing of Fig 5A.

Figure 5B shows records from a patient with chronic otitis media with perforated eardrum. In this case, tympanoplasty I had been performed with a postauricular incision, and postoperative infection caused perforation. A silver ball electrode was set at the promontorium through the perforated eardrum, and the record was taken under the same conditions as in the acoustic neurinoma case. To obtain PAR, differential electrodes were placed at the mastoid portion of the operated ear. There were clear biphasic waves in the recording of the promontorium electrode; however, there were no such waves in the postauricular region, as seen at the lower tracing (myogenic response) of Fig 5B. The biphasic response evoked from the promontorium was an SEMG.

DISCUSSION

In the present study, with ECoG, the stapedius muscle innervated by the facial nerve showed a biphasic wave caused by acoustic stimuli.

Fisch and Schulthess[11] reported an EMG study of human stapedius muscle. During surgery, they exposed the stapedius muscle, inserted a microelectrode, and observed the change of units obtained from the muscle by varying the sound pressure level of the contralateral stimulus. According to their report, although the latency varied as the sound pressure level was changed, it was always around 11 ms.

In our experiment, SEMG latency was 11.09 ms during ipsilateral stimulation and 10.09 ms during contralateral stimulation. These were similar to the values reported by Fisch and Schulthess[11] and seemed reasonable. Yoshie and Okudaira[5] reported that the latency of PAR was around 13 ms. Bochenek and Bochenek[1] reported that PAR was around 13 ms, and that the latency changed in facial paralysis according to the degree of the lesion. As the stapedius muscle is closer to the facial nucleus than the postauricular muscle, it is natural that its latency is shorter. The change of SR amplitude is parallel to the degree of contraction of the stapedius muscle.

Borg[7] performed simultaneous unit recordings of stapedius muscle EMGs and SRs in cats. He integrated the increase of units at different sound pressure levels, compared the integrated values with the SR values obtained by the impedance method, and found that they increased in parallel.

In our study, the frequency increase of units corresponded to the amplitude of the biphasic wave. The EMG amplitude showed good linearity with the SR amplitude, and the correlation ratio for all the cases was 0.855.

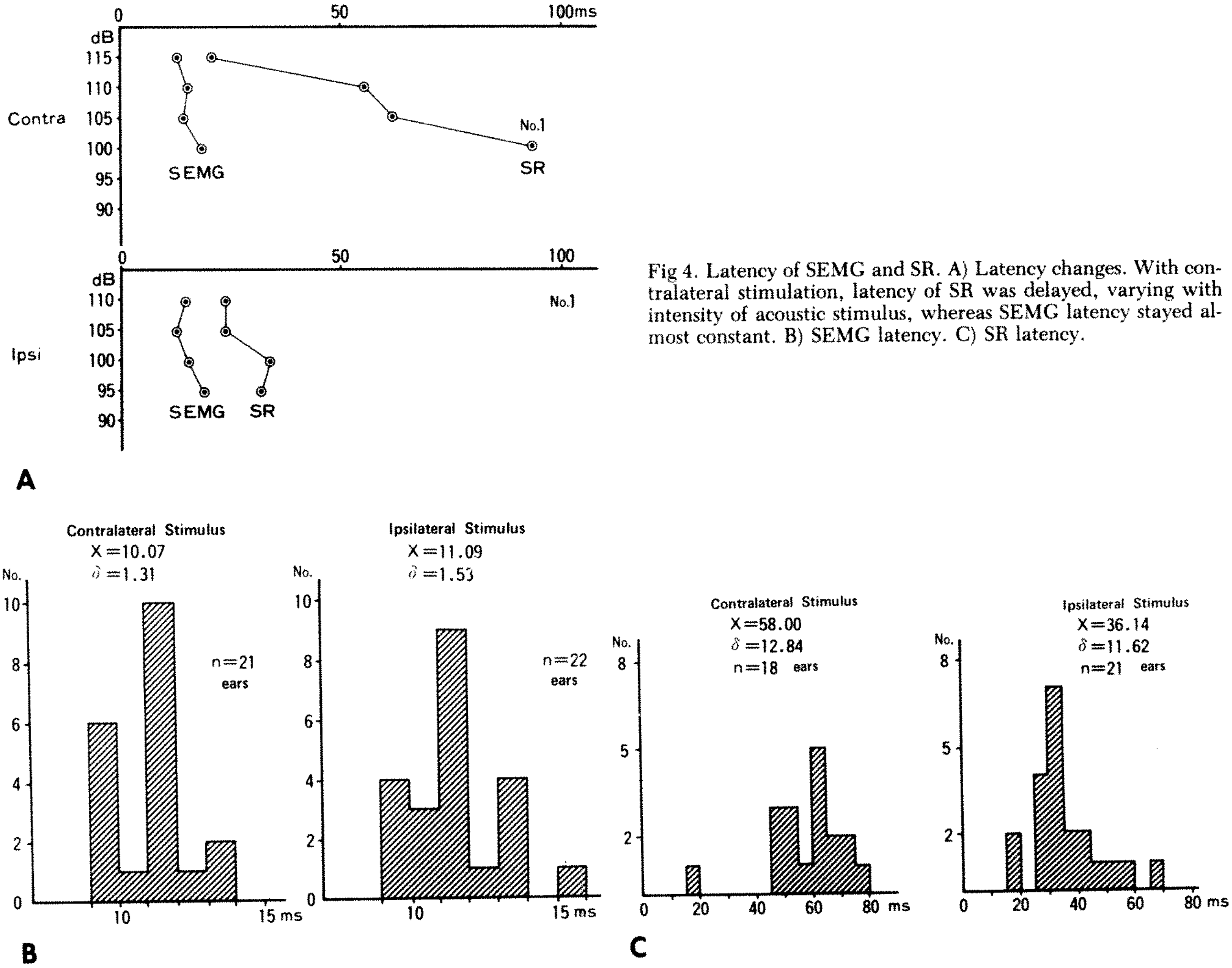

Fig 4. Latency of SEMG and SR. A) Latency changes. With contralateral stimulation, latency of SR was delayed, varying with intensity of acoustic stimulus, whereas SEMG latency stayed almost constant. B) SEMG latency. C) SR latency.

A loud acoustic stimulus evokes a PAR as an acoustic facial reflex. Since the voltage difference between the earlobe and the eardrum was recorded in the present method, some mixing of SEMG with PAR might occur in normal cases. In order to avoid this, it is desirable to pick subjects with no postauricular muscle or postauricular nerve. The second patient in our study had no postauricular muscle or nerve, since a postauricular incision had been performed. When a silver ball electrode was placed at the promontorium, a large biphasic wave still was observed.

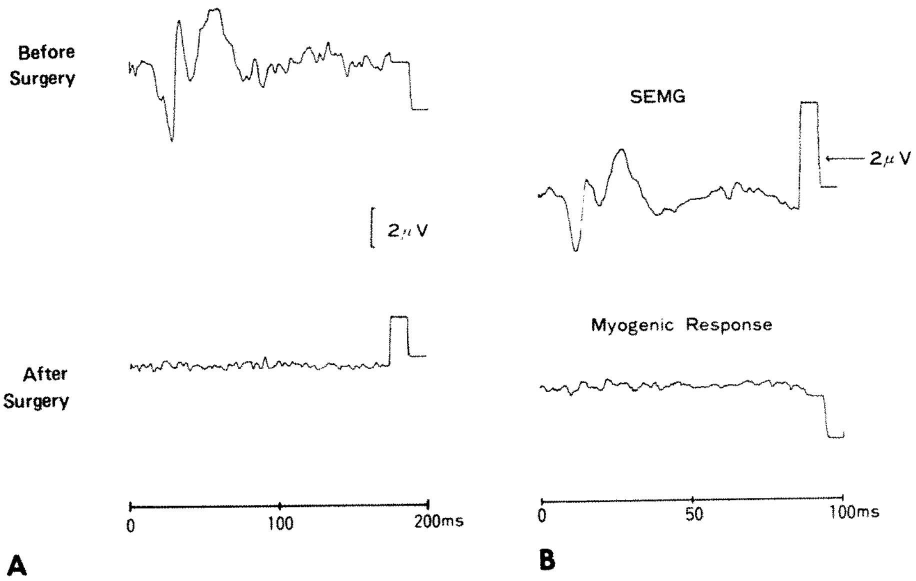

Fig 5. A) SEMG of patient with acoustic neurinoma showing clear biphasic wave with 14-ms latency. After surgery there was complete facial paralysis due to facial nerve injury, and no waves were observed in EMG recording. B) Postoperative infection after tympanoplasty I resulted in perforation of eardrum. SEMG recordings evoked from promontorium had dominant biphasic waves, but no clear waves were present in recordings from postauricular region.

When a lesion, either central or peripheral, interrupts the acoustic facial reflex system, especially if the lesion is in a motor branch of the facial nerve, it is presumed that latency or amplitude changes of the biphasic waves may occur. Complete facial paralysis was caused by the removal of an acoustic neurinoma, and the biphasic waves disappeared. Hence there is evidence that the biphasic wave represents stapedius muscle contraction.

An SEMG has a more constant latency under various levels of acoustic stimuli than does the SR latency. Even in normal subjects, the SR latencies varied with the strength of the acoustic stimuli. The SR latency was prolonged in cases of acoustic neurinoma, depending on the size of the lesion on this reflex pathway.[14-16]

Jerger and Hayes[15] recommended measuring the SR latency of acoustic neurinoma in three different ways: 1) at equal hearing levels, 2) at equal sound pressure levels, and 3) at equal SR amplitudes. As seen in the present experiment, it is clear that the latency is delayed as the hearing levels change. Therefore, in comparing right and left latencies, it is desirable to make the hearing levels equal.

On the other hand, SEMG latency is obviously constant. In normal subjects, it did not change even when hearing levels were varied. In the patient with acoustic neurinoma described above, the latency was about 14 ms — an obvious delay. It is easier to measure the latency of biphasic EMG waves than that of SR waves. Hence measurement of the SEMG latency is quite useful in the detection of lesions in the reflex pathway.

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Ann Otol Rhinol Laryngol 97:1988

X-RAY STUDY OF THE MONTH

CEREBROSPINAL FLUID SEROUS OTITIS MEDIA

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CASE REPORT

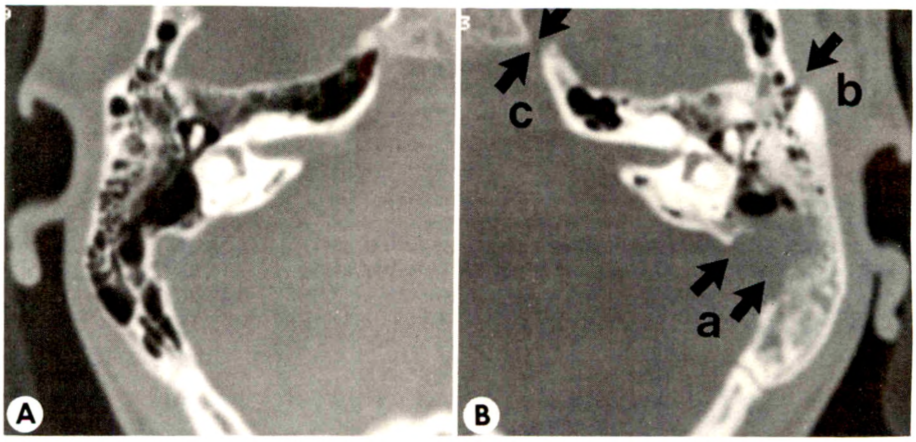
A 13-year-old boy was wounded in the face by a 22-caliber bullet. The path of the bullet coursed through the preauricular region, right external auditory canal, and right cerebellar hemisphere and lodged in the right occipital lobe. On physical examination, he was alert and oriented. The facial nerve was intact; however, a homonymous hemianopsia was present. Debridement and exploration of the wound revealed no bullet fragments. There was a large tear in the right external ear canal and an intact tympanic membrane and hemotympanum. Outpatient visits revealed a persistent mild hearing loss and intermittent dizziness. His visual defects resolved. He was noted to have a persistent right serous otitis media without otorrhea. An audiogram was remarkable for a right 10-dB conductive hearing loss and shallow tympanogram. High resolution computed tomography of the temporal bone was performed to locate a defect that could result in a CSF leak.

RADIOGRAPHIC FINDINGS

The CT scan showed opacification of the right mastoid and middle ear cavities (see Figure, B). There was disruption of the right anterior mastoid bone in the region posterior to the external auditory canal and close to the sigmoid sinus. The fluid in the mastoid cavity appeared to be in continuity with the posterior fossa. The anterior portion of the fracture was anterior to the attic along the outer temporal surface, and there was slight separation of the petrous apex and the adjacent sphenoid bone. Exploration of the right mastoid cavity revealed a small amount of free fluid. The anterolateral portion of the sigmoid sinus was dehiscent and covered with dense scar tissue. Upon palpation of the scar tissue, a small CSF leak was noted. A fascial plug was sewn over the leak, and a temporalis fascial graft was sutured over the plug. Then a temporalis muscle flap was swung into the mastoid cavity and sutured into place. A lumbar drain was placed, and the patient had an uneventful recovery. He was discharged on the ninth postoperative day. The serous otitis media resolved and has not recurred.

DISCUSSION

The majority of CSF leaks associated with trauma close spontaneously and require observation only. The rich vascular supply of the underlying arachnoid mesh usually seals the dural rent within 24 to 48 hours.[1] The true incidence of traumatic CSF leaks is not known. It has been estimated that 2% of all cases of head trauma are complicated by persistent CSF drainage.[1] The CSF leak presents as otorrhea, otorhinorrhea, rhinorrhea, or serous otitis media.[2] If the injury is of such magnitude that neu-



Computed tomographs. A) Normal left ear and mastoid bone. B) Right ear and mastoid cavity showing some opacification of middle ear and mastoid air cells. Longitudinal fracture oriented transversely to petrous ridge is shown. a — posterior portion of fracture in mastoid antrum near sigmoid sinus, b — anterior portion of fracture, peripheral and anterior to attic, c — separation of petrous apex and sphenoid bone.

From the Division of Pediatric Otolaryngology, Department of Otolaryngology–Head and Neck Surgery, Washington University, St Louis. Dr Seligman is now in the Division of Otolaryngology–Head and Neck Surgery, University of Chicago.

rosurgical intervention is required, dural tears are repaired during exploration and persistent leaks are prevented. Bony fragments, created at the time of injury, may entrap the arachnoid and dura. The poor approximation of the soft tissue during the healing process results in a persistent fistula. If a sinus tract develops in the temporal bone, the CSF drains into the middle ear. If the drum is intact and the eustachian tube is patent, the CSF may flow into the nasopharynx unnoticed, except for intermittent positional rhinorrhea. High resolution CT is invaluable in identifying areas of bony disruption. If the site of leakage is not obvious, radioisotope or serial high-pressure metrizamide CT may be performed. Because of the high infection rate associated with persistent CSF leak, every effort should be made to secure a watertight seal. If dural edges cannot be approximated precisely, temporalis fascia, fascia lata, fat graft, absorbable gelatin sponge or film, cortical bone chips, oxidized cellulose, freeze-dried dura, or acrylic compounds may be used.[3,4] There are two surgical approaches to the repair of a CSF leak. One is intracranial, providing access to the posterior or middle cranial fossa superior to the petrous ridge. The other is transmastoid, permitting repair of the defect from below, using whatever soft tissue is desired for the patch. If herniating brain tissue is encountered, it may be safely amputated as it is nonfunctional.[5] Once the leak is sealed, the mastoid cavity is packed with fat or a temporalis muscle pedicle flap to reinforce the closure. Neurosurgical consultation should be obtained in the event that a craniotomy or postoperative lumbar subarachnoid drain is required to seal the defect.

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INTERNATIONAL WORKSHOP ON CRANIO-FACIAL TRAUMA

An International Workshop on Cranio-Facial Trauma will be held October 9-14, 1988, in Adelaide, South Australia. The workshop is sponsored by the Australian Cranio-Maxillo-Facial Foundation. For further information, contact Mrs D. Moody, Executive Officer, 226 Melbourne Street, North Adelaide SA 5006, Australia.

Ann Otol Rhinol Laryngol 97:1988

PATHOLOGY CONSULTATION

SIALADENOSIS

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Sialadenosis, characterized by a uniform hypertrophy and hyperplasia of the acinar parenchyma of salivary glands, is associated with a variety of systemic diseases or functional disorders. Present evidence relates the clinical and morphologic changes in the salivary tissues to a neuropathic alteration of the autonomic innervation of the salivary acini.

Sialadenosis or sialosis of salivary glands belongs in the differential diagnosis of bilateral and, far less often, unilateral swellings of the parotid glands. The disorder is a noninflammatory parenchymatous disease brought about by a secretory and metabolic disturbance of the acinar parenchyma.[1] In most instances, sialadenosis presents as a painless, recurrent bilateral swelling of the parotid glands.

Because of the conspicuous (50%) association of sialadenosis with disorders of the nervous system, altered nutritional states, endocrinopathies, and pharmacologic effects of medication, it has been classified into three major groups: neurogenic, dystrophic-metabolic, and hormonal.[1,2] Experimental evidence points to a dysregulation of the autonomic innervation of the salivary acini as the unifying factor in all forms of sialadenosis.[1,3,4]

With the exceptions of the vasodilator action of bradykinin and the stimulation of ductal sodium and potassium transport by aldosterone, physiologic control of the salivary glands is effected nearly solely by the autonomic nervous system.[1,4,5] Quantitatively, the human parotid gland is furnished equally with both sympathetic and parasympathetic fibers. The morphologic secretory cycle of production, accumulation, and secretion within the acinar cell is dependent on regulated neurostimulation and is influenced by the daily rhythm of intake of food. The transfer of secretory stimulation occurs via α and β receptors on the membranes of acinic cells (see Table).

The heterogeneous and seemingly disparate synchrotic disorders (starvation, malnutrition, force-feeding, alcoholism, bulimia, anorexia nervosa, diabetes mellitus, ovarian and thyroid diseases, hepatic disorders)[1,2,5-7] associated with sialadenosis all produce their salivary effects through an aberrant intracellular secretory cycle within the acinar cell. The abnormality of the cycle is a result of a neurohormonally elicited interference on the neuroreceptor of the glandular cell.

Changes in the secretory behavior of an acinus can be caused either by an excessive stimulation or by an inhibition of secretion, both initiated through a neuropathic alteration in the autonomic innervation of the the acini.[1,3] With this in mind, sialadenosis can then be considered a result of a peripheral autonomic neuropathy.[8]

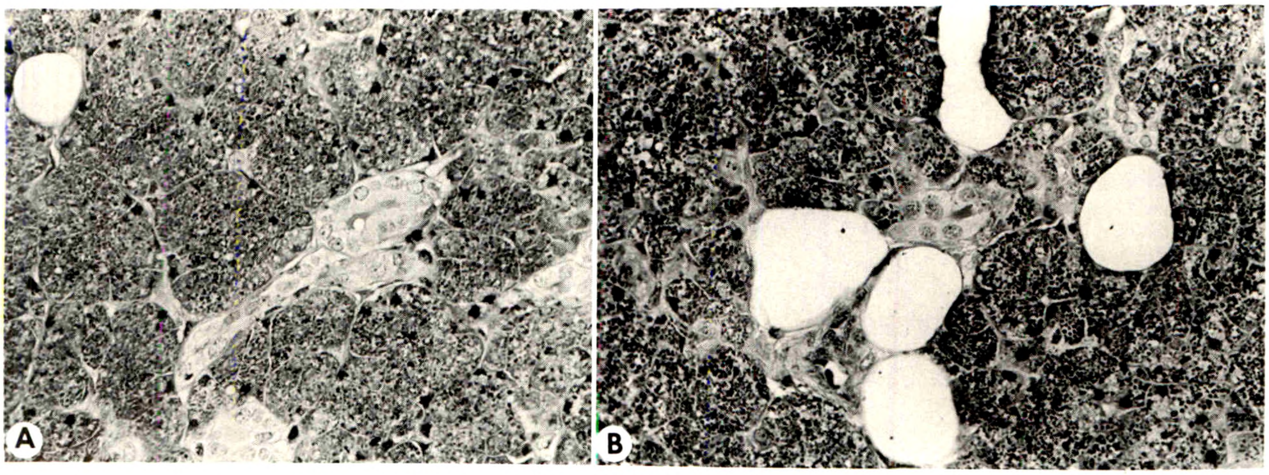
Biopsy specimens from humans and parotid sections from experimental animals with sialadenosis, either stimulatory or inhibitory in type, characteristically manifest an increased acinar diameter[1,3,8,9] (see Figure, A). Control parotid acini have a mean diameter of 30 μm. Sialadenotic acini have diameters of up to 100 μm.[9] There is uniform hypertrophy and likely a hyperplasia of the functional acinar parenchyma. The cytoplasm of the swollen acinar cells is either granular, alveolate-translucent, or a mixture of both (see Figure, B). Ultrastructurally, the secretory granules of different optical densities correspond to the light-optic cytoplasmic structure. Donath and Seifert[9] have distinguished three different types of sialadenosis on the basis of electron-optic appearances: dark granular, light granular, and mixed granular. The dark granular cells mani-

SEQUENCE OF EVENTS LEADING TO SYMPATHETIC-PARASYMPATHETIC INNERVATION OF SALIVARY ACINUS

Action potential in presynaptic cell
↓
Depolarization of plasma membrane of presynaptic axon terminal
↓
Release of neurotransmitter by terminal
↓
Chemical combination of transmitter with specific receptors on cell plasma membrane
↓
Conductance changes of plasma membrane
↓
Changes in membrane potential
↓
Initiation of secretory cycle in cell

From the University of Texas M. D. Anderson Hospital and Tumor Institute at Houston.

REPRINTS — John G. Batsakis, MD, Division of Pathology, M. D. Anderson Hospital, Texas Medical Center, Houston, TX 77030.



Sialadenosis of parotid gland in A) 42-year-old male alcoholic (H & E, original x150). Note enlarged acini filled with secretory granules. B) Higher magnification of acini from same patient (H & E, original x500). Although granules are preponderantly optically dense, some are clear or reticulated.

fest protein-rich granules but are without evidence of an increased synthesis of proteins. Granules of low optical density and increased synthesis of protein characterize the light granular type. It should be noted, however, that there is no correlation between these electron-optic forms and the clinical presentations of the sialadenosis. It is likely that intrinsic differences in the secretory cycle of the acini and their autonomic control account for the predominance of the parotid glands as afflicted sites in sialadenosis.

Few observations have been made on the stromal-parenchymal ratio in parotid glands in sialadenosis. In the early stages of experimentally induced sialadenosis, it is said to be unaltered.[3,9] In the human, however, an unremitting or uncorrected autonomic neuropathy (eg, long-standing alcoholism or diabetes mellitus) should eventuate in atrophy of the acini and lipomatous replacement.

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VII IBEROLATINAMERICAN CONGRESS OF PLASTIC SURGERY

The VII Iberolatinamerican Congress of Plastic Surgery will be held May 22-28, 1988, in Cartagena, Colombia. For further information, contact Sociedad Colombiana De Cirugia Plastica, Ap Aereo Nos. 6658/6572, Bogota DE, Colombia, SA.

LETTERS TO THE EDITOR

To the Editor:

I read with interest Dr Harold Schuknecht's supplement (Temporal Bone Collections in Europe and the United States. *Ann Otol Rhinol Laryngol* 1987;96[suppl 130]). In the section "Pathologic Findings of Clinical Relevance" (pp 16-18), a very important statement is made on the causative relationship between acute otitis media and meningitis. Despite the fact that this statement makes sense and I can support it with clinical observations, the relevant supporting bibliography is not included and I did not find it in my records. If the data were published, I would like to ask the courtesy of Dr Schuknecht in indicating it.

Four years ago I diagnosed bilateral purulent acute otitis media in a 3-month-old infant. Needle aspiration was performed. A few hours later meningitis was diagnosed. The bacteriologic culture of the middle ear effusions, CSF, and peripheral venous blood yielded *Streptococcus pneumoniae*, serotype 14, indicating most probably a hematogenous spread as suspected by Dr Schuknecht.

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To the Editor:

The reference and abstract for the statement referred to in the letter from Dr Ostfeld is as follows: Eavey RD, Gao Y-Z, Schuknecht HF, Gonzalez-Pineda M. Otologic features of bacterial meningitis of childhood. *J Pediatr* 1985;106:402-7. "Sixteen temporal bones from eight children who had died of meningitis were histopathologically evaluated. Concurrent acute otitis media was demonstrated in 14 bones. In no case could a pathway of infection from the tympanomastoid compartment to the intracranial cavity be located. Further, inner ear infection appeared to be the result of retrograde bacterial invasion from the meninges rather than from an inoculation via the middle ear or mastoid. Should surgical drainage be required, the histopathologic findings indicate that mastoidectomy would have little advantage over myringotomy. We infer that a child with normal temporal bone anatomy is probably not at enhanced risk for development of bacterial meningitis from acute otitis media via a route of direct extension."

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BOOK REVIEWS

Manual of Otolaryngology–Head and Neck Therapeutics

Arnold E. Katz, ed. Hard cover, illustrated, indexed, 531 pages, 1986. Lea & Febiger, Philadelphia.

Dr Katz's objective in compiling and editing the material in this text was not to add to the armamentarium of the otolaryngologist–head and neck surgeon. Instead, it was to give recognition to the importance of the medical management of these patients and to make available to those physicians less well trained in this field the significance of clinical findings and the options in treatment. Toward his objective, Dr Katz selected as contributors to this text 34 specialists in various fields who have expertise in the treatment of a particular otolaryngologic or head and neck problem. Their material is presented in outline form, which facilitates the extraction of the information that is pertinent to a given medical situation.

The title of this book may be somewhat misleading: it accurately describes the work as a manual, but seemingly limits the contents to therapeutics. This book obviously is not intended to be used as a "take-this-for-that" Merck manual, but the word therapeutics does indicate methods to be used in healing or treatment. In actuality, therapies are for the most part dealt with in generalities and without discussion. On the other hand, this book could be described quite accurately as a diagnostic teaching manual and as such compares very favorably with similar compendiums. Indeed, some of the chapters present good insight into pathogenesis. As might be expected in this type of text, the information given is general, but in most cases it is certainly adequate for the intended reader (ie, medical student, first year resident, primary care physician).

The material is timely and well presented. The data are accurate and unencumbered by details that might be desired by the highly trained otologist or otolaryngologist–head and neck surgeon. The major limitation in this presentation is the scarcity of illustrations. Tables are used well throughout the book and provide excellent accessory information to the basic concepts provided in the chapters. Nevertheless, for those physicians in the editor's stated target of readers, an appropriately and adequately illustrated text conveys far more information than does written material alone. Overall, however, this manual is an excellent tool for those who require only a fundamental concept of otolaryngology.

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Ear, Nose and Throat Disorders in Children

J. E. Bordley, P. E. Brookhouser, and G. F. Tucker, Jr. Hard cover, illustrated, indexed, 446 pages, 1986. Raven Press, New York, $47.50.

The authors have combined their expertise in an attempt to write a comprehensive volume that discusses otolaryngologic disorders in children. The book is interdisciplinary in its approach, as it is written by an eminent laryngologist, an expert in communication disorders in children, and an experienced pediatric otolaryngologist. According to the preface, the book is "designed as a compact reference book that will be useful to pediatricians, general practitioners, resident trainees in otolaryngology, pediatrics, family practice and medical students."

The main strength of this volume is its extensive and detailed discussion of otologic disorders in infants and children, which encompasses the first half of the text. The chapters discussing measurement of hearing, vestibular assessment, and speech and language disorders are more comprehensive and better presented than those in most standard otolaryngologic textbooks. These sections of the textbook are especially recommended to the otolaryngology resident.

The second half of the book discusses the remaining areas of pediatric otolaryngology and includes the nose and accessory nasal sinuses, mouth and pharynx, neck, and larynx. Some shortcomings of the textbook are found here. While the text is intended to be a reference book, many subjects are covered tersely and are not quite as up-to-date as the discussions of these topics in several major general pediatric and otolaryngologic textbooks. Treatment options are not discussed in detail, although the authors state in the preface that "surgical intervention and surgical reconstruction are discussed in general terms so that the attending doctor can understand the underlying rationale and be better prepared to discuss the surgery with the patient."

In summary, the volume is recommended as a reference source to pediatricians and general practitioners and would be a valuable addition to libraries of residency training programs in otolaryngology–head and neck surgery. The experienced pediatric otolaryngologist or practicing otolaryngologist with extensive experience in pediatrics may find the book somewhat elementary.

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Otolaryngology-Head & Neck Surgery

Charles W. Cummings, John M. Fredrickson, Lee A. Harker, Charles J. Krause, David E. Schuller, eds. Vols 1-4. Hard cover, illustrated, indexed, 3,558 pages, 1986. CV Mosby, St Louis, $325.95.

In these four volumes, outstanding clinicians in otolaryngology-head and neck surgery present their expertise under the astute editorial guidance of Dr Cummings. While the reader is cautioned appropriately to refrain from accepting any one source as authoritative and absolute, the qualifications of the contributors are certainly exemplary. Their intent is to provide contemporary textbooks in which the most current information related to otolaryngology-head and neck surgery is presented. Four physicians proficient in this field of medicine were asked to review this extensive material, which is clearly delineated in four broad areas, each in a separate volume. Our reviewers found the texts to be well organized and referenced, with adequate illustrations. Recognizing that no single publication will meet the criteria of every individual reader, our reviewers judged each volume to be an excellent addition to the literature currently available on this topic.

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Birmingham, Alabama

Vol 1. General Face, Nose, Paranasal Sinuses

The avowed aim of the editors of this work was to write a contemporary comprehensive textbook in the field of otolaryngology. The editors state that their goal was to produce a definitive work and thus to provide a foundation for continued progress in the field by future generations. These aims were indeed lofty, but the textbook lives up to its mission extremely well. The book is designed as a reference for both practitioners and residents.

The first volume alone is about 1,000 pages. As in the other volumes, a multiauthor format is used. All authors are well-chosen and respected experts in the fields on which they have written. It is obvious that considerable care went into their selection. The fact that the editors were able to convince the leaders in our specialty to contribute a chapter to yet another textbook indicates that there is a strongly perceived need for this text and a belief that the volumes would succeed as a major reference.

The book begins with a section on general considerations in the area of the head and neck. The section includes chapters on areas such as diagnostic imaging, antimicrobial therapy, staging, and skin flap physiology. There are also chapters on special considerations in different age groups. The remainder of volume 1 is divided into sections on the face, nose, and paranasal sinuses. In each of these areas, the book is subdivided so as to begin with chapters on the relevant basic science, after which it continues with sections on diagnostic assessment, clinical entities, and special considerations.

The appropriate use of illustrations is a significant asset of this book. Each volume carries an index for all four volumes, a major advantage for a reference text. The references are listed alphabetically at the end of each chapter, and the list is generally comprehensive. I personally would prefer to see them listed numerically according to their order in the text, but this is a minor complaint.

As chapters are written by authors who have a special love for their own fields, they are informative and comprehensive. There are few significant gaps in the areas presented, and repetition between chapters, a major potential problem with multiauthored books, is minimal. In some situations, however, tighter editorial control might have reduced the length of individual chapters. In one or two instances a controversial or questionable statement has been allowed to pass unreferenced. It is difficult to believe, for instance, that gravity plays a significant role in the preferential occurrence of orbital blowout fractures in the inferior orbital wall, particularly in the absence of supportive evidence or referencing.

This volume succeeds admirably in its aim to be a definitive reference text for practicing otolaryngologists and residents. Overall, the four volume set appears to constitute the most comprehensive reference work within the specialty. There are no major shortcomings with this text — an outstanding achievement for a first edition of this magnitude. This is clearly work that will be around for many years and will provide a major contribution to the specialty. I would recommend it highly as the most up-to-date and comprehensive work for practitioners and residents within the specialty.

DAVID W. KENNEDY, MD
Baltimore, Maryland

Vol 2. Salivary Glands, Oral Cavity/Oropharynx, Neck

Volume 2 was written to provide the practicing otolaryngologist or resident with a complete, thorough reference source for the treatment of both medical and surgical problems encountered in these areas. This book will be of value to any practitioner dealing with head and neck disease, thoroughly covering anatomic considerations and physiology. Thorough discussions of both pertinent physical examination and appropriate diagnostic imaging techniques are given. Infectious diseases, metabolic disturbances, neoplastic processes, and trauma that may involve the structures of the salivary glands, oral cavity, and oropharynx, as well as the neck, are covered in detail. The depth of coverage of each topic is most appropriate. Topics are well indexed, and a very thorough reference guide is provided at the end of each topic's coverage. The illustrations are instructive and clearly diagramed. All of the material presented was well organized and presented in a readable fashion, allowing the reader to quickly locate and grasp any points of information needed. This book would make an excellent addition to the library of the otolaryngology-head and neck practitioner or resident. This book compares favorably with similar publications and perhaps examines most topics in greater depth than similar publications currently available.

M. ALAN GOODSON, MD
Birmingham, Alabama

Vol 3. Larynx/Hypopharynx, Trachea/Esophagus, Thyroid/ Parathyroid

Although not stated in volume 3, a review of the contents of all volumes indicates the intention of the authors to provide a contemporary, state-of-the-art textbook for the medical community in the rapidly expanding subspecialty of otolaryngology-head and neck surgery. Based on the contents of volume 3, I believe that the authors have achieved their objective.

Subdivision 1 in each volume is entitled Basic Science. This section describes the anatomy and physiology of the organ system to which the volume relates. In volume 3, I found the descriptive anatomy and accompanying diagrams adequate but not outstanding. In view of the scope of subject matter covered, however, detailed anatomic drawings may not be practical. Based on the color plate of the larynx that opens the volume, I cannot but wonder if the addition of more detailed anatomic colored plates would improve the reader's comprehension, particularly in the laryngeal and thyroid sections.

The section on physiology of the larynx details the underlying principles of swallowing and phonation, with a very interesting and unique section on laryngeal research by Donald Cooper. The section on laryngeal functions in speech is comprehensive and well written but lacks supporting dynamic diagrams.

Subdivision 2, Diagnostic Assessment, documents the important facts and techniques related to the history and physical examination. This area is the cornerstone in the assessment of any diagnostic problem and should be stressed particularly to the medical student and house officer. This subject is discussed adequately in the laryngeal section, but is poorly detailed in the esophageal/tracheal and thyroid sections. As expected, the sections on diagnostic testing are emphasized, with high marks going to neurodiagnostic testing of the larynx. Radiographic anatomy is well documented with appropriate clinical examples. Radiology of the hypopharynx and esophagus by Heiken are complete and excellent. The chapters on radiology of the larynx and trachea are comprehensive, with outstanding illustrations, but fail to discuss the value, indications, and limitations of the radiographic techniques as related to the pathologic states discussed.

Subdivision 3, Clinical Entities, divides disease into congenital, infectious, traumatic, and neoplastic areas. An additional chapter on local manifestations of systemic disease is excellent, as are most of the other sections. If I were to choose a weak chapter, I would cite the section on laryngeal trauma as being too abbreviated.

Subdivision 4, Special Considerations, is truly a unique feature of this book. It would be impossible for me to discuss each of the subjects covered in this section. Some of the outstanding chapters that deserve special mention include The Professional Voice by Sataloff, Conservation Surgery of the Larynx by Schecter, Airway Management by Weymuller, and Surgical Management of Parathyroid Disorders by Wang. This section points out the difficulty of selecting authors and subject matter that avoid the bias of individual research interests. A basic text must protect the initiate who may not be able to separate fact from fancy. "Near total laryngectomy" is undoubtedly an excellent technical achievement, but its acceptance by the head and neck community as a standard of care has not been established. The chapter entitled Tracheostenosis is well organized and complete, except for the section on surgical repairs, which is brief and poorly illustrated. Some chapters on surgical technique should stress the indications, limitations, and contraindications of surgery in a more formal and didactic manner.

It is my opinion that volume 3 is a suitable textbook for the medical student and resident in otolaryngology and related specialties. The reader of this text, as of any text, must reject authority and question the knowledge gained by further study and reading. No textbook can completely avoid personal bias or controversial statements. With the few exceptions mentioned, I applaud the authors for constructing a new and excellent text. I recommend this for one's personal library as a valuable basic review text. Since the purchase of this four-volume set is a relatively expensive investment, it would be worthwhile for the reader to compare this text with other new or updated textbooks with a similar format and subject matter. No single text will fulfill everyone's needs.

Richard L. Fabian, MD
Boston, Massachusetts

Vol 4. Ear and Skull Base

Volume 4 acknowledges the coming of age of skull base surgery by its subtitle. It has been edited by Lee A. Harker and comprises some 900 pages organized into 49 chapters written by 51 primary and 21 associate authors, all but a few of whom are academically based. Thirty-six major institutions are represented. This volume contains an average of 12 illustrations per chapter, which were prepared by multiple illustrators. There are four color plates, one an elegant frontispiece appropriately showing the temporal bone in skull base orientation. The editors' stated goals in producing the four-volume set were to produce a definitive contemporary reference text suitable for residents and practitioners alike, and in so doing to acknowledge significant contributions that have been made to the specialty.

Technically, this volume is attractive and well produced. Basic elements such as paper, print, and ink appear to be of high quality and allow for comfortable reading. Heading styles are uniform and also contribute to ease in reading. Surprisingly few typographic and spelling errors are noted. Illustrations are in general clearly reproduced, but there are a few unfortunate exceptions in which color illustrations converted to black and white have failed to provide adequate detail. Using multiple illustrators for this volume has not produced a significant problem with style. Reproductions of x-ray films are generally of very high quality. The table of contents is well organized into sections on basic science, diagnosis, external ear, middle ear/temporal bone, inner ear, and skull base. Overlapping coverage has been avoided for the most part. The index is extensive and provides multiple tracks to a desired subject in most cases.

I have the impression that the authors of this volume have been selected for their particular expertise and ability to express themselves clearly, rather than for geographic convenience. The editor and the publisher have obviously worked overtime to see that a comfortable and relatively uniform style was achieved.

Regarding specific content, this volume is generally excellent, particularly for a first edition. There are some subjects that might benefit from additional material or from modification of approach. Meniere's disease, otalgia, and carcinoma of the temporal bone are topics that might benefit from the addition of more clinically directed information, but these are exceptions. Two real gems contained in this volume are sections on the surgical treatment of otosclerosis by Brian McCabe, and an overview of skull base surgery by William House. In each case, the reader will have the feeling that he or she has had a conversation with the author, rather than simply read his material.

With few exceptions, the chapters are well referenced. I would have liked to have seen references following the first chapter, on temporal bone anatomy, but there were none. Four chapters had no illustrations, and I felt there were situations in which several carefully chosen illustrations would have enhanced comprehension of the subject matter. The basic science chapters on anatomy and physiology of hearing and balance were scholarly and of particularly high quality. The chapter on mastoid surgery was particularly well illustrated, and perhaps led me to wish for a few more illustrations for other surgical chapters, without turning this into an atlas.

The goal of the editors to recognize contributions that have been made to otolaryngology was accomplished to a high degree. Exceptions that I noticed were that no credit was given to John Shea in the area of otosclerosis, and none to either David Austin or to Lloyd Storrs for their contributions to tympanoplasty. Very little was mentioned concerning early contributions to audiology. Again, however, these were distinct exceptions.

It has never been easy to produce a comprehensive yet readable textbook for a discipline such as otolaryngology. It is perhaps more difficult now than ever. This particular volume has been well produced, and I believe will serve well the needs of today's otolaryngologists.

Gale Gardner, MD
Memphis, Tennessee

AMERICAN SOCIETY OF PEDIATRIC OTOLARYNGOLOGY

1988 Preliminary Program

(Subject to change)

Kiawah Island, South Carolina

Wednesday to Saturday (April 20 to 23), mornings

Anterior cricoid split, 1977-1987: evolution of a technique. C. M. Myer, MD

Comparison of the similarities and differences between the anterior cricoid split operation in humans and in animal models. C. W. Senders, MD

A study of hydroxylapatite in the treatment of acquired subglottic stenosis. R. Miller, MD

Voice quality following laryngotracheal reconstruction. D. Kearns, MD

Subglottic stenosis and Down's syndrome. S. Gray, MD

Broken Aboulker stents in the tracheal lumen. G. Zalzal, MD

Kawasaki syndrome: an update for the pediatric otolaryngologist. M. April, MD

Pediatric neck masses: guidelines for evaluation. L. Tom, MD

Adenoiditis in children. A. Turner, MD

Unusual branchial anomalies. D. Snyder, MD

Management of congenital preauricular cysts and sinus tract in children. S. Prasad, MD

Nasal and oropharyngeal dimensions in children with obstructive sleep apnea. L. Brodsky, MD

Obstructive sleep apnea syndrome in sickle cell anemia disease. B. Maddern, MD

Potential for airway compromise following adenotonsillectomy in children with sleep apnea. E. Harley, MD

Congenital nasal pyriform aperture stenosis. O. Brown, MD

Choanal atresia: a protocol for the diagnosis, treatment, and evaluation of results. W. M. Belenky, MD

Clinical experience with electroneuronography in the pediatric patient. R. D. Eavey, MD

Facial paralysis in children. J. A. Herzog, MD

Contraindications to exploration of the facial nerve in traumatic paralysis in children. C. S. Durkey, MD

Basilar skull fractures in children. D. B. Hawkins, MD

Fluctuating or progressive sensorineural hearing loss in children. P. Brookhouser, MD

Mixed sensorineural and conductive hearing loss in children. K. Grundfast, MD

Disorders of hearing associated with congenital cytomegalovirus infection. F. I. Catlin, MD

Otitic candidiasis in children: an evaluation of the problem and effectiveness of ketoconazole in ten patients. S. R. Cohen, MD

Fluctuating hearing losses in children can be migraine equivalents. P. Bernard, MD

Otological manifestations in congenital velopharyngeal insufficiency. R. Shapiro, MD

Comparative evaluation of amoxicillin and Ceclor in treatment of acute otitis media with effusion. J. Stanievich, MD

Intellectually gifted adolescents: academic and behavioral correlates. P. Brookhouser, MD

High resolution ultrasonography of the parotid gland in children: part II. J. Seibert, MD

Magnetic resonance imaging of the neck: applications in pediatric otolaryngology. D. Crockett, MD

Sternocleidomastoid muscle tumors of infancy. P. Koltai, MD

The drooling patient — a 10-year experience. W. Crysdale, MD

HIV protocol for the pediatric otolaryngology office. H. Muntz, MD

Craniofacial approach for the management of congenital frontal encephaloceles. G. Gussack, MD

Alveolar soft part sarcoma of the head and neck: a disease of children and young adults. W. B. Simmons, MD

Gaining access to school for the child with a tracheotomy — a model program. K. Grundfast, MD

Bacterial tracheitis in children. J. Donaldson, MD

Laryngeal foreign bodies in children. J. Lima, MD

Severe laryngomalacia. Constellation of associated diseases. J. Erdman, MD

Congenital circumferential tracheal rings. G. Milmoe, MD

Endobronchial tuberculosis in children. G. Wood, MD

Recognition and management of chronic sinusitis in infants and children: a report of 75 children. R. Bogdasarian, MD

COMBINED OTOLARYNGOLOGICAL SPRING MEETINGS

1988 Preliminary Programs

(Subject to change and Council approval)

The Breakers, Palm Beach, Florida

AMERICAN NEUROTOLOGY SOCIETY

Friday, April 22 (all day); Saturday, April 23 (afternoon)

The neurotologic patient — early clinical assessment and diagnostic problems. J. L. Pulec, MD

Significance of audiologic and vestibular findings. F. H. Linthicum, Jr, MD

Radiologic examination — polytomography and Pantopaque myelography. B. H. Britton, MD

Cerebellar pontine angle lesions — the Otologic Medical Group experience. W. F. House, MD

Acoustic tumor surgery — the Danish experience. J. Thomsen, MD

Skull base surgery — its evolution. M. E. Glasscock III, MD

Computerized axial tomography and magnetic resonance imaging in the diagnosis of lesions of the skull base. G. E. Valvassori, MD

Auditory brain stem responses — evolution and significance in contemporary neurotologic diagnosis. D. E. Brackmann, MD

Electroneuronography and intraoperative monitoring in contemporary neurotologic surgery. J. M. Kartush, MD

Theoretical bases for the design of tests of smooth pursuit and optokinetic nystagmus reflex function. J. Lin, MD; V. Honrubia, MD

On the search for markers of impaired compensation after vestibular surgery. B. Blakley, MD; H. O. Barber, MD; M. Mai; S. Stoyanoff; D. Tomlinson

Comparison of dynamic posturography and caloric test results in patients with vertigo. J. Goebel, MD; G. Paige, MD

Evidence of central vestibulo-auditory dysfunction in Cogan's syndrome: a case report. J. T. Benitez, MD; M. D. Arsenault, MA; J. M. Licht, MD; S. D. Cohen, MD; R. V. Greenberg, MD

Benign paroxysmal positional vertigo — a correlation of vestibular modalities. D. I. Bojrab, MD; J. M. Kartush, MD; C. W. Stockwell, PhD; M. D. Graham, MD

Patterns of dynamic posturography. M. A. Hamid, PhD, DIC; G. B. Hughes, MD; K. Haddon

Is there consensus in perilymph fistula management? G. B. Hughes, MD; A. Sismanis, MD; J. W. House, MD

Specific diagnostic testing in autoimmune inner ear disease. J. P. Harris, MD, PhD; R. I. Fox, MD

Use of acoustic facial EMG monitoring during facial nerve rerouting in infratemporal fossa surgery. R. L. Prass, MD; D. E. Brackmann, MD; A. De La Cruz, MD

The usefulness of 1,000-Hz tone burst-evoked responses in the diagnosis of acoustic neuroma. S. A. Telian, MD; P. R. Kileny, PhD

Clinical differentiation of facial electromyographic activity during skull base surgery. P. G. Smith, MD, PhD; E. T. Mishler, MA; J. L. Peterein, MS

Disabling tinnitus: association with affective disorder. M. D. Sullivan, MD, PhD; R. A. Dobie, MD; W. Katon, MD; C. Sakai, MSPA; J. Russo, MA; H. Harrop-Griffiths, MBBS

Morphology of the cochlear nerve before and after stimulation by the cochlear implant. L. Terr, PhD; J. Sfogliano

Preservation of hearing following 6-mm intracochlear implantation for tinnitus: a case report. C. M. Luetje, MD; P. Arndt, MA

Surgical implantation and tolerance of a CNS auditory neuroprosthesis. J. K. Niparko, MD; D. J. Anderson, PhD; X. Xue, MS; R. A. Altschuler, PhD; J. L. Kemink, MD

Tonotopic organization of intracochlear nerve. D. M. Lee, MD; F. H. Linthicum, Jr, MD

Long-term hearing results following middle fossa vestibular nerve section. M. E. Glasscock III, MD; G. D. Johnson, MD; D. S. Poe, MD

Long-term results of cochleovestibular neurectomy for treatment of vertigo. H. Silverstein, MD; R. Jones, MD; E. Smouha, MD

Infralabyrinthine approach to the internal auditory canal. D. M. Vernick, MD

Transmastoid labyrinthectomy — a reliable surgical management of vertigo. J. L. Kemink, MD; S. A. Telian, MD; M. D. Graham, MD

Cavernous hemangiomas of the internal auditory canal. D. G. Pappas, MD; D. E. Brackman, MD; L. C. Simpson, MD

Total facial nerve decompression for recurrent facial paralysis: an update. M. D. Graham, MD; J. M. Kartush, MD; D. I. Bojrab, MD

Aneurysmal cyst of the temporal bone. D. B. Kamerer, MD; B. E. Hirsch, MD

Survival of the vestibular nerve following labyrinthectomy in the cat. S. P. Cass, MD; C. W. Stockwell, PhD; P. Davidson; H. G. Goshgarian, PhD

Spinal fluid profile following surgery in the subarachnoid space. P. S. Roland, MD; W. L. Meyerhoff, MD, PhD; K. Belcombe, MD; B. Mickey, MD

Hearing preservation in acoustic neuroma surgery. B. Blakley, MD; J. M. Nedzelski, MD; D. W. Rowed, MD

Preservation of hearing in central neurofibromatosis. R. T. Miyamoto, MD; R. L. Campbell, MD; M. Fritsch, MD; G. Lochmueller, MD

Cochlear nerve conduction block: an explanation for spontaneous hearing return after acoustic tumor surgery. J. F. Kveton, MD

Is there a conductive type of presbycusis? H. Ramadan; H. F. Schuknecht, MD

Survival of human spiral ganglion cells in profound sensorineural hearing loss. J. B. Nadol, Jr, MD

Immunohistochemical evidence of measles virus antigens in active otosclerosis. M. J. McKenna, MD; B. G. Mills, MD

High resolution magnetic resonance imaging in evaluating multiple sclerosis. J. F. Norfray; A. B. Devlesc Howard; H. R. Konrad; D. C. Good; R. M. Bass

Unilateral meningitis labyrinthitis: a new radiographic correlate. B. H. Britton, MD

The use of magnetic resonance imaging in conjunction with high resolution computed tomographic scans for the evaluation of facial paralysis patients. M. K. Schwaber, MD; M. Seshul, MD; R. H. Ossoff, DMD, MD; J. L. Netterville, MD

Paraneoplastic syndromes associated with glomus tumors of the skull base. C. G. Jackson, MD; M. E. Glasscock III, MD; G. W. Know, MD; A. J. Gulya, MD; M. L. Pensak, MD; D. S. Poe, MD; G. D. Johnson, MD

Intraneural, extracranial extension of a glomus tumor. L. J. Bartels, MD; P. Rice, MD; J. Pennington, MD

Glomus vagal tumors: the significance of early vocal cord paralysis. J. P. Leonetti, MD; D. E. Brackmann, MD

Entrapment injury of the facial nerve secondary to longitudinal fracture. L. R. Grobman, MD; A. Pollack, MD; U. Fisch, MD

AMERICAN OTOLOGICAL SOCIETY, INC

Saturday, April 23 (morning); Sunday, April 24 (afternoon)

Vestibular atelectasis. S. Merchant, MD; H. F. Schuknecht, MD

Clinical diagnosis of AICA thrombosis — autopsy and temporal bone histopathological study. R. Hinojosa, MD; R. I. Kohut, MD

Selective lesions of the vestibular labyrinth. R. S. Kimura, PhD

Osteogenesis imperfecta and its relation to otosclerosis. G. T. Nager, MD

MR of the posterior cranial fossa. G. E. Valvassori, MD

Differential clinical and radiographic features of cholesterol granulomas and cholesteatomas of the petrous apex. P. G. Smith, MD, PhD; G. R. Kletzker, MD; A. P. K. Wild, MD

Adenomas of the temporal bone. T. L. Eby, MD; M. S. Makek, MD; U. Fisch, MD

Preoperative embolization of vascular tumors of the ear and skull base. R. J. Wiet, MD; E. Russell, MD; E. M. Monsell, MD, PhD; N. M. Young, MD

Anatomical considerations in hearing conservation procedures in management of acoustic neuromas. P. S. Roland, MD; W. L. Meyerhoff, MD, PhD; C. G. Wright, PhD

Preservation of hearing in acoustic tumor surgery: audiologic indicators. A. Forrest Josey, MS; M. E. Glasscock III, MD; C. G. Jackson, MD

The gamma knife — an alternative treatment for acoustic neurinomas. D. B. Kamerer, MD; L. D. Lunsford, MD

Vestibular rehabilitation: basic principles and illustrative cases. M. A. Hamid, PhD; K. Szirony

Otologic manifestations of patients with AIDS. D. Kohan, MD; S. G. Rothstein, MD; N. L. Cohen, MD

One thousand deaf children: their characteristics and concomitants. L. Bergstrom, MD

Major congenital ear malformations: surgical management and results. P. R. Lambert, MD

Multichannel implants in a partially ossified cochlea. T. J. Balkany, MD; J. B. Nadol, MD

Medical/surgical complications related to Nucleus multichannel cochlear implant. N. L. Cohen, MD; R. A. Hoffman, MD; M. Stroschein, MD

Experiences with the Nucleus multichannel implant in three young children. W. Luxford, MD; W. House, MD; J. Hough, MD; L. Tonokawa; K. Berliner, PhD; E. Martin

An implantable middle ear hearing device — ongoing animal and human evaluation. J. Hough, MD; K. J. Dormer, PhD; R. S. Baker, MD; M. Meikle, PhD

A preliminary study on the middle ear implantable hearing aid. A. J. Maniglia, MD; W. H. Ko, PhD; R. Zhang, EE

The incidence of cholesteatoma with cleft palate. S. Dominguez; L. Harker, MD

Is cholesteatoma the same disease in children and adults? D. Edelstein, MD; S. C. Parisier, MD; G. S. Bindra, MD; C. Juarbe, MD; V. Moradia, MD; G. S. Ahuja, MD; J. C. Han, MD; P. Chute, MA

The role of osteoclasts in middle ear disease. R. A. Chole, PhD

Surgical treatment of cholesteatoma — open versus closed operations. G. D. L. Smyth, MD

Intact bridge tympanomastoidectomy in the treatment of chronic suppurative middle ear disease. M. M. Paparella, MD; R. L. Nissen; M. Morris; R. Fox

Hearing restoration in tympanosclerosis. D. F. Austin, MD

Otologic complications following temporomandibular joint arthroscopy. L. F. Berg, MD; M. F. Mafee, MD; A. Kumar, MD; E. L. Applebaum, MD

AMERICAN LARYNGOLOGICAL ASSOCIATION

Saturday, April 23 (afternoon); Sunday and Monday, April 24 and 25 (mornings)

Endoscopy and the KTP laser for nasal sinus disease. H. Levine, MD

Video nasopharyngoscopy — a comparison of fiberscopic, telescopic and microscopic documentation. E. Yanagisawa, MD; S. Emucha, MD; R. Hirokawa, MD

Magnetic resonance imaging of the head and neck: when and why? R. A. Atiyah, MD; M. R. Fisher, MD; G. A. Sisson, Sr, MD

Choanal atresia: treatment trends in 47 patients over 33 years. J. L. Ferguson, MD; H. B. Neel III, MD

The histopathology of sleep apnea. C. P. Kimmelman, MD; J. S. Brooks, MD; V. A. LiVolsi, MD; R. P. Millman, MD

Scintigraphic assessment of gastroesophageal reflux in the head and neck patient. D. B. Kuriloff, MD; P. Chodosh, MD; F. Ongseng, MD; R. Goldfarb, MD

Light microscopic analysis of human laryngeal epithelium during the fetal period. S. R. Schaffer, MD; J. A. Tucker, MD

The laryngeal chemoreflex: an anatomic study of the peripheral receptor in the piglet. R. M. Esclamado, MD

Sectional anatomy of the larynx: implications for the percutaneous approach to endolaryngeal structures. R. J. Lipton, MD; T. V. McCaffrey, MD; D. R. Cahill

Asymmetry of the laryngeal framework. A morphological study of cadaver larynges. M. Hirano, MD; S. Kurita, MD; K. Yukizane, MD; S. Hibi, MD

A new system for the quantification of hoarseness. D. Kohan, MD; K. L. Schneider, MD; P. Gittelman, MD; S. Breda, MD

The effect of topical anesthesia on vocal cord motion. D. A. Drezner, MD; M. L. Ronis, MD; R. M. Mohr, MD

Laryngeal synkinesis: its significance to the laryngologist. R. L. Crumley, MD

A comparison of the effect of Teflon and Phonogel on laryngeal vibration in simulated recurrent nerve paralysis. T. K. Trapp, MD; G. S. Berke, MD; T. S. Bell, PhD

The effects of cricoid muscle contraction on laryngeal resistance and glottic area. G. E. Woodson, MD; F. Sant'Ambrogio; O. Matthew; O. Sant'Ambrogio

Observations on the pathophysiology of voice disorders. C. N. Ford, MD; D. M. Bless, PhD

Patient and family perception of voice and speech following severe laryngeal trauma and surgical reconstruction. M. D. Trudeau, PhD; D. E. Schuller, MD; D. Portman

Voice restoration following laryngectomy: the role of primary versus secondary transesophageal puncture. B. I. Wenig, MD; V. M. Mullooly, RN; J. Levy, MA; A. L. Abramson, MD

Botulinum toxin for the treatment of oromandibular dystonia. A. Blitzer, MD; M. F. Brin, MD; S. Fahn, MD

Botulinum toxin to lateralize one vocal cord. S. R. Cohen, MD

Laryngeal framework surgery in the management of spasmodic dysphonia. H. M. Tucker, MD

Treatment of spastic dysphonia with an implantable nerve stimulator. M. Friedman, MD; D. M. Toriumi, MD; V. Grybauskas, MD; E. L. Applebaum, MD

Contraction time, strength of contraction, and fatigue in the reinnervated thyroarytenoid muscle. D. H. Rice, MD; D. S. Cooper, PhD

Newer technique of laryngeal reinnervation. A. J. Maniglia, MD; N. Kumar, MD; K. Sorensen, MD; B. Kutirji, MD

Surgical correction of dysphonia due to bowing of the vocal cords. J. A. Koufman, MD

Laryngotracheoplasty — indications and pitfalls. M. D. Maves, MD; B. F. McCabe, MD

Advantages of the rotary door flap in laryngeal-tracheal reconstruction — is skeletal support necessary? I. Eliachar, MD; J. Roberts, MD; H. M. Tucker, MD

The primary management of laryngeal trauma: an update. S. D. Schaefer, MD; L. G. Close, MD

Management of laryngeal burns. M. L. Cheney, MD; W. W. Montgomery, MD; P. B. Flexon, MD; P. L. Turner

Glomus vagali tumors. H. F. Biller, MD; W. Lawson, MD

Cartilaginous tumors of the trachea and larynx. P. R. Neis, MD; M. F. McMahon, MD; C. W. Norris, MD

Tumor growth and extension in the larynx. L. W. Welsh, MD

Clinical management of recurrent respiratory papillomatosis: a study of interferon alfa-N1 in mild/moderate disease. G. A. Singleton, MD; K. Clark; M. A. Richardson, MD; H. H. Dedo, MD; H. K. Kashima, MD; B. Levanthal; A. J. Yonkers, MD; H. R. Muntz, MD; P. K. Weck

Ventral cleft of the larynx. J. A. Schild, MD; M. F. Mafee, MD

Model of a new generation of tracheostomy and endotracheal tubes. J. A. Rao, MD; C. R. Aiyer, MD; T. Komatsu, MD; Y. Shimada, MD; N. Yanagita, MD; S. Hattori, MD

Laser epiglottectomy: endoscopic technique and indications. S. Zeitels, MD; C. W. Vaughn, MD; G. T. Simpson, MD

Laser surgery for vocal cord carcinoma involving the anterior commissure. Y. P. Krespi, MD; C. J. Meltzer, MD

Computerized tomography in patients with laryngeal carcinomas: a clinical perspective. J. Werber, MD; F. E. Lucente, MD

Flow cytometric analysis of laryngeal carcinomas. G. S. Gussack, MD; W. Hudson, MD; L. Pratt, MD

The natural history of treated T1N0 epidermoid carcinoma of the laryngeal glottis. T. N. Kaiser, MD; D. G. Sessions, MD; J. E. Harvey, PhD

Squamous cell carcinoma of the thyroid: a diagnostic dilemma. G. S. Korovin, MD; D. B. Kuriloff, MD; H. T. Cho, MD; S. M. Sobol, MD

The utility of the near total laryngectomy for cancer of the supraglottic larynx, pharynx and sites other than the glottic larynx. L. W. DeSanto, MD; K. D. Olsen, MD; B. W. Pearson, MD

Adenosquamous carcinoma of the larynx and hypopharynx. G. L. Adams, MD; K. K. Aden, MD; H. Fattah, MD

Partial laryngectomy and radiotherapy for supraglottic cancer: a conservative approach. C. A. Spaulding, MD; W. C. Constable, MB, ChB; R. W. Cantrell, MD

Isolated pulmonary nodules in head and neck cancer patients. J. Sercarz, MD; D. E. Ellison, MD; E. C. Holmes, MD; T. C. Calcaterra, MD

Definitive radiotherapy in the management of stage I and stage II carcinomas of the glottis. M. D. Kelly, MD; C. R. Kersh, MD; W. C. Constable, MB; S. S. Hahn, MD; R. W. Cantrell, MD

Subtotal resection of the thyroid cartilage for laryngeal radionecrosis. J. A. Koufman, MD

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Monday, April 25 and Tuesday, April 26 (afternoons)

Chevalier Jackson Lecture. What would Chevalier Jackson think? L. Hill, MD

Broyles-Maloney research speaker. The development of mini-endoscopes: state of the art. R. Kozarek, MD

Pediatric tracheotomy — a 10-year review. R. I. Feldman; W. S. Crysdale, MD, FRCS(C)

Tracheal resection in children. G. B. Healy, MD; S. R. Schuster, MD; R. Jonas, MD

Anatomic findings and management of choanal atresia associated with the CHARGE association. A. S. Hengerer, MD

Congenital stenosis of the lower esophagus associated with leiomyomata and leiomyosarcoma of the gastrointestinal tract: a report of a family. S. R. Cohen, MD; N. Sherman, MD

Dilation of esophageal strictures: comparative morbidity of antegrade and retrograde methods. D. B. Hawkins, MD

Experience with tracheal-laryngeal separation for intractable aspiration. C. Snyderman, MD; J. T. Johnson, MD

Indications for the tracheoesophageal diversion procedure and the laryngotracheal separation procedure. D. W. Eisele, MD; C. T. Yarington, Jr, MD; R. C. Lindeman, MD

Tracheal invasion by thyroid carcinoma. D. D. Lydiatt, DDS, MD; D. T. Jones, MD; F. P. Ogren, MD; A. J. Yonkers, MD

Computed tomography in determining laryngeal involvement of hypopharyngeal carcinoma. M. Hirano, MD; S. Kurita, MD; J. S. Cho, MD; H. Tanaka, MD

Obstructing tumors of the subglottic larynx and cervical-tracheal airway management and treatment. S. M. Shapshay, MD; R. K. Bohigian, MD; J. F. Beamis, Jr, MD

The upper aerodigestive tract manifestations of cicatricial pemphigoid. R. D. Hanson, MD; K. D. Olsen, MD; R. S. Rogers, MD

Prospective study of subglottic stenosis in intubated neonates. K. M. Grundfast, MD; F. Camilon, MD; S. Pransky, MD; C. S. Barber, MD; R. Fink, MD

Rib cartilage grafts for the treatment of posterior glottic and subglottic stenosis in children. G. H. Zalzal, MD

The use of the composite nasal septal graft for the treatment of laryngeal and laryngeal-tracheal stenosis. J. A. Duncavage, MD; R. H. Ossoff, MD; R. J. Toohill, MD

An assessment of prolonged intubation trauma using a portable videolaryngoscopy system. D. M. Alessi, MD; D. G. Hanson, MD; G. Berci, MD

Thyroglossal duct remnants in infants and children: re-evaluation of the histopathology and methods for resection. M. A. Hoffman, MD; S. R. Schuster, MD

The "saber-sheath" trachea. E. J. Callan, MD; E. V. Karandy, MD; R. L. Hilsinger, Jr, MD

The evaluation of laryngeal calcium deposition: a new methodology. H. M. Yerman, MD; J. Werkhaven, MD; J. A. Schild, MD

Hypocalcemia following pharyngoesophageal ablation and gastric pull-up reconstruction: pathophysiology and management. J. C. Price, MD; M. B. Ridley, MD

Acute epiglottitis in adults. L. Shih, MD; D. B. Hawkins, MD; R. B. Stanley, MD, DDS

AIDS and the broncho-esophagologist. F. E. Lucente, MD; L. Z. Meiteles, MD

Laryngeal framework surgery in the management of the aged larynx. H. M. Tucker, MD

Acute airway obstruction due to necrotizing tracheobronchial aspergillosis in immunocompromised patients: a new clinical entity. N. T. Berlinger, MD, PhD

Pneumothorax as a complication of tracheoesophageal voice prosthesis. R. M. Odland, MD; G. L. Adams, MD

Near-fatal complications of tracheal T-tube use. K. H. Calhoun, MD; R. Deskin, MD; B. J. Bailey, MD

Management of a clavicular-tracheal fistula secondary to osteoradionecrosis of the sternoclavicular joint. G. M. Stofman, MD; L. D. Lowry, MD; J. R. Cohn, MD

Lateral pharyngeal diverticula. D. O. Mikaelian, MD; D. Drosnes, MD; J. Stark, MD

A universal ventilation laser tracheoscope. S. M. Shapshay, MD; J. F. Beamis, Jr, MD; E. McDonald

A new laryngeal tracheal stent: internal support without loss of speech capability. I. Eliachar, MD; J. Roberts, MD; H. M. Tucker, MD

Adult subglottiscope for carbon dioxide laser surgery. R. H. Ossoff, DMD, MD; J. A. Duncavage, MD

Fiberscoptic video nasopharyngolaryngoscopy — a low cost portable system. E. Yanagisawa, MD; S. Kmucha, MD

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Tuesday to Thursday (April 26-28), mornings

Human immunodeficiency virus and sensorineural hearing loss. A. F. Bell, MD; J. S. Atkins, Jr, MD

Effects of long-term ablation of the endolymphatic sac in the vervet monkey. J. Swart, MD; H. F. Schuknecht, MD

The diagnosis and management of cerebrospinal fluid leak. M. S. Persky, MD; S. G. Rothstein, MD; S. D. Breda, MD; N. L. Cohen, MD; P. Cooper, MD; J. Ransohoff, MD

Congenital stenosis — concepts of diagnosis and treatment. M. M. Paparella, MD; M. Morris, MD; H. Sajjadi, MD; O. Sousa, MD

Intact canal wall tympanoplasty with mastoidectomy for cholesteatoma: long-term follow-up. S. E. Kinney, MD

Comparison of benefits given by a single-channel, vibrotactile aid and a multichannel, multi-electrode, intracochlear implant to a postlinguistically deaf adult. M. W. Skinner, PhD; S. M. Binzer, MA; J. M. Fredrickson, MD; P. G. Smith, MD, PhD; T. A. Holden; L. K. Hull, MA; M. F. Juehlich, MA

Performance of five different cochlear implant designs. B. J. Gantz, MD; B. F. McCabe, MD; R. Tyler, PhD; N. Tye-Murray, PhD; F. Kuk, PhD; J. Knutson, PhD; P. Abbas, PhD

Magnetic resonance imaging. W. L. Meyerhoff, MD; P. S. Roland, MD; B. Mickey, MD

Facial nerve function following irradiated cable grafts. W. F. McGuirt, MD; B. Welling, MD; B. F. McCabe, MD

Functional endonasal surgery in the pediatric age group. C. W. Gross, MD; M. Gurucharri, MD; T. E. Long, MD; R. H. Lazar, MD

Endoscopic nasal sinus surgery. D. H. Rice, MD; M. B. Tom, MD

Review of 670 Caldwell-Luc procedures from 1975-1985. F. E. Lucente, MD; J. DeFreitas, MD

Fatal and major complications following nasal and sinus surgery. A. J. Maniglia, MD

Isolated uvulitis secondary to marijuana use. J. L. Guarisco, MD; M. L. Cheney, MD; H. T. Reed, MD; F. E. LeJeune, Jr, MD

Head and neck procedures: are they DRG money-makers? V. Mullooly, RN, MS; A. L. Abramson, MD

Indications for tonsillectomy and adenoidectomy: changing trends. R. P. Green, MD; R. M. Rosenfeld, MD

Nocturnal enuresis and upper airway obstruction. D. J. Weider, MD; M. Sateia, MD; P. Hauri, PhD

Surgical management of severe laryngomalacia. L. D. Holinger, MD; R. J. Konior, MD

Orbital decompression for dysthyroid exophthalmopathy: an analysis of 338 cases. R. Bunde, MD; J. G. Spector, MD; J. D. Warren, MD

A new needle and technique for MR-guided aspiration cytology of the head and neck. T. K. Trapp, MD; R. Lufkin, MD; W. Hanafee, MD; L. Layfield, MD; P. H. Ward, MD

In vitro tests in the diagnosis and management of allergy. D. J. Nalebuff, MD

Analysis of IgG RAST as a diagnostic tool in food allergy. A. S. Rapoport, MD

Preoperative assessment of parotid masses: comparative evaluation of different radiologic techniques. M. Byrne, MD; J. G. Spector, MD; M. Gado, MD; C. Garvin, MD

Reflux laryngopharyngitis as an etiological factor of carcinoma of the larynx and pharynx. P. H. Ward, MD

Further experience with botulinum toxin for spasmodic dysphonia. R. H. Miller, MD; G. E. Woodson, MD; J. Jankovic, MD

Nerve transfer versus Teflon injection for vocal cord paralysis: a comparison. R. L. Crumley, MD

Surgical pathology of cancer of the oral cavity and oropharynx. C. Brennan; D. G. Sessions, MD; J. Harvey, PhD

Transoral CO_2 laser excision of oral cavity and oropharynx squamous cancers — cancer treatment results and complications. C. Mamikunian, MD; S. L. Collins, MD

Octapressin: a vasoconstrictor equipotent with epinephrine. W. F. Larrabee, Jr, MD

Radiation-induced fibrosarcoma of the mandible. P. J. Moloy, MD; K. K. Miyamoto

Osteomyelitis of the frontal bone. W. W. Montgomery, MD; M. L. Cheney, MD; E. E. Jacobs, MD

The optimal treatment for small tongue cancers. K. T. Robbins, MD; R. M. Byers, MD; L. Carlson, MD; J. G. Batsakis, MD

Preoperative chemotherapy in advanced resectable head and neck cancer — final report of the Southwest Oncology Group. D. E. Schuller, MD; B. Metch, MS; D. W. Stein, MD

A direct approach to the base of the skull. J. Conley, MD

Three-dimensional computed tomography for craniofacial and laryngeal surgery. S. J. Zinreich, MD; M. E. Johns, MD; J. C. Price, MD; M. J. Holliday, MD; H. K. Kashima, MD

Paranasal sinus malignancy: the Northwestern experience. D. M. Toriumi, MD; G. A. Sisson, MD

Surgical resection for recurrent nasopharynx cancer. W. E. Fee, Jr, MD; P. A. Gilmer, MD

Sublabial transseptal transsphenoidal hypophysectomy. D. W. Eisele, MD; P. W. Flint, MD; J. D. Janas; E. A. Weymuller, Jr, MD; W. A. Kelly, MD; C. W. Cummings, MD

Computer fabricated custom mandibular replacement prostheses. J. C. Price, MD; J. Zinreich, MD

Pectoralis major myocutaneous flap reconstruction of the pharynx and cervical esophagus after extended laryngectomy. R. L. Fabian, MD

Tissue expansion and delayed bridge separation in forehead flap nasal reconstruction. S. S. Kroll, MD

External rhinoplasty with tip grafts for reconstruction of the cleft lip nasal deformity. W. E. Hagen, MD

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Soft tissue changes associated with orthognathic surgery: cervical angle. L. E. Costa II, DMD, MD

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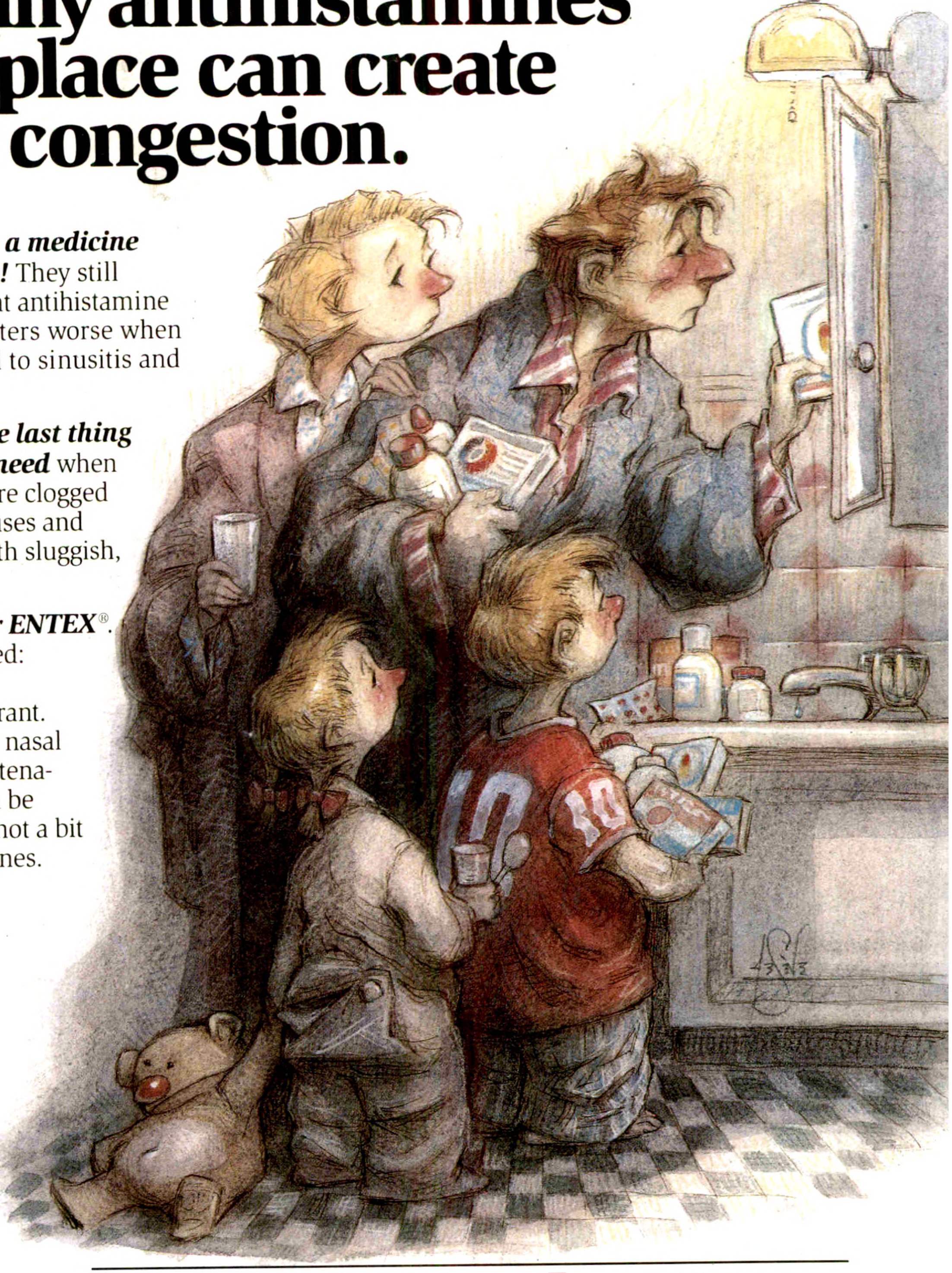

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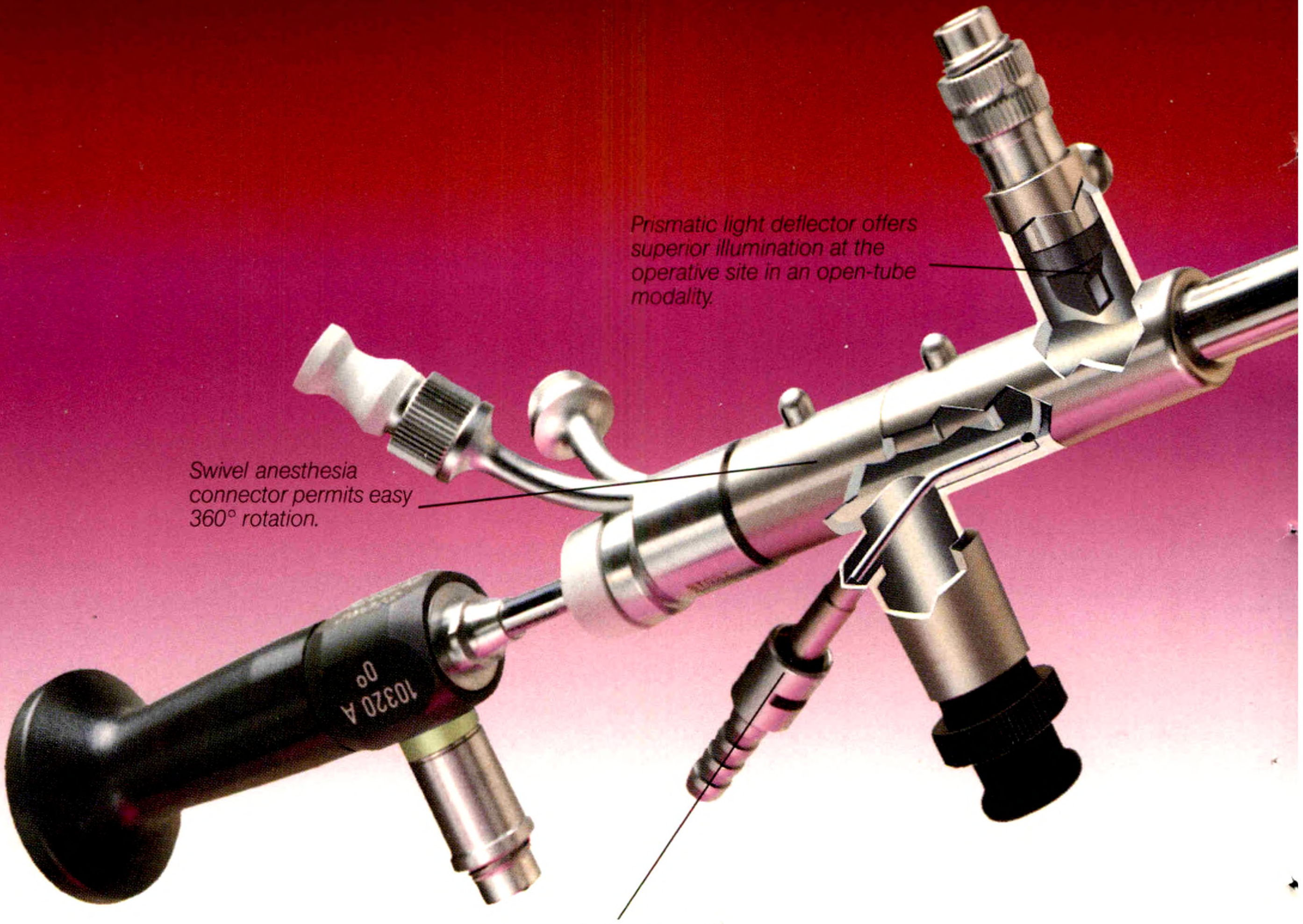
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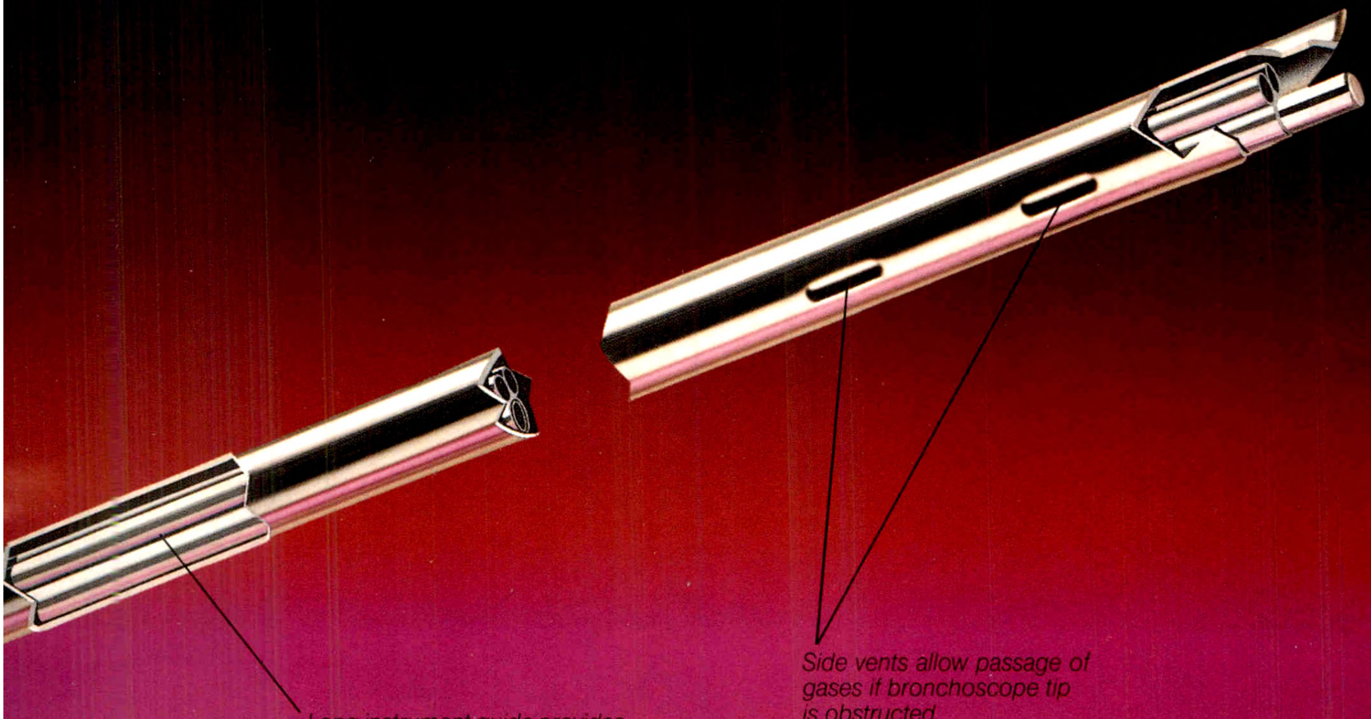

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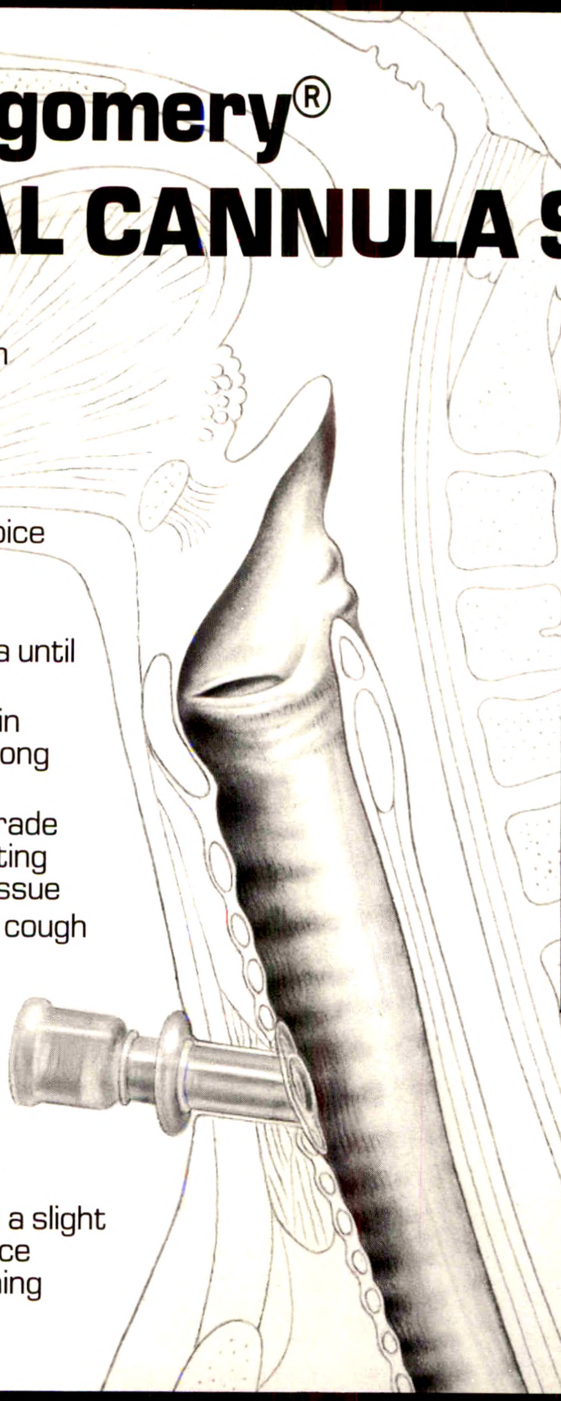

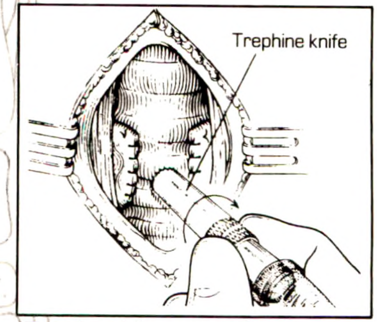

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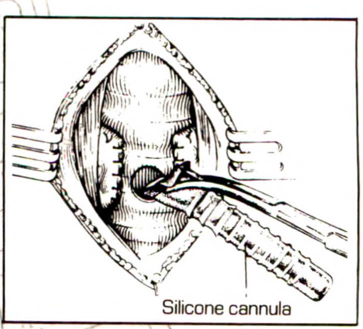

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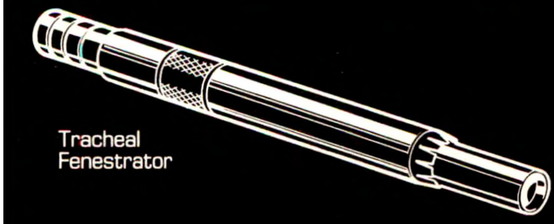

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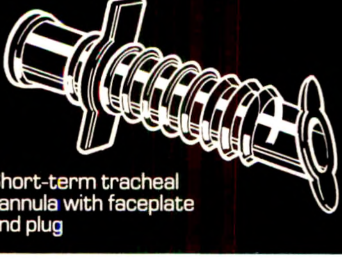

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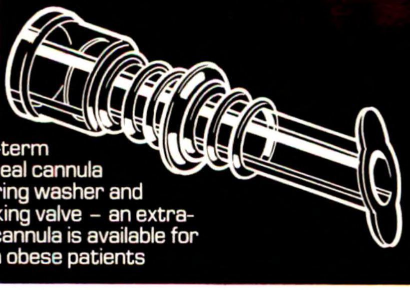

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CONTENTS

PART 1

Perilymph Fistula: The Stanford Experience
Clough Shelton, MD; F. Blair Simmons, MD 105

Stapedectomy Trends for the Resident
Newton J. Coker, MD; Newton O. Duncan III, MD; Geoffrey L. Wright, MD; Herman A. Jenkins, MD; Bobby R. Alford, MD 109

Airway Management of Acute Supraglottitis at the Children's Hospital, Boston: 1980-1985
Dennis M. Crockett, MD; Gerald B. Healy, MD; Trevor J. McGill, MD; Ellen M. Friedman, MD 114

The Tricyclic Trimipramine in the Treatment of Subjective Tinnitus
R. Clifford Mihail, MD; Joanne M. Crowley, MA; Brian E. Walden, PhD; Joseph Fishburne, PhD; John E. Reinwall, PhD; Joan T. Zajtchuk, MD 120

Antenatal Diagnosis of Congenital Deafness
Glenn Isaacson, MD 124

Reduction of Salivary Flow With Scopoderm TTS
Yoav P. Talmi, MD; Yehuda Finkelstein, MD; Yuval Zohar, MD; Nelu Laurian, MD 128

Aural Pain Resulting From Acoustic Reflex
Stephen W. Painton, PhD; Michael B. Shaw, DO 131

High Frequency Audiometry in Prospective Clinical Research of Ototoxicity due to Platinum Derivatives
R. J. A. M. van der Hulst, MD; W. A. Dreschler, PhD; N. A. M. Urbanus, MD 133

Depression of T Cells in Bell's Palsy
Lars Jonsson, MD; Olof Sjöberg, MD, PhD; Lars Thomander, MD, PhD 138

Prospective Study of the Effects of Ventilation Tubes on Hearing After Radiotherapy for Carcinoma of Nasopharynx
C. R. Chowdhury, FRCS; J. H. C. Ho, MD, DSc; A. Wright, FRCS; S. Y. Tsao, FRCR; G. K. H. Au, FRCR; Y. Tung, MBBS 142

Auditory and Vestibular Disorders due to Barotrauma
Tsutomu Nakashima, MD; Michio Itoh, MD; Yusuke Watanabe, MD; Masahiro Sato, MD; Noriyuki Yanagita, MD 146

Effect of Anti-inflammatory Drugs on Collagen-Induced Autoimmune Inner Ear Disease
Naohiro Sudo, MD; T. J. Yoo, MD, PhD 153

Effects of Stripping and Laser Excision on Vocal Fold Mucosa in Cats
Rebecca J. Leonard, PhD; Louis J. Gallia, MD, DDS; George Charpied, MS; Andrew Kelly, DVM 159

Acoustic Analysis of Voices of Patients With Neurologic Disease: Rationale and Preliminary Data
Lorraine A. Ramig, PhD; Ronald C. Scherer, PhD; Ingo R. Titze, PhD; Steven P. Ringel, MD 164

Acute Effects of Irradiation on Middle Ear Mucosa
Yoshihiro Ohashi, MD; Yoshiaki Nakai, MD; Yusuke Esaki, MD; Hiroshi Ikeoka, MD; Hiroyuki Koshimo, MD; Yasuto Onoyama, MD 173

Adductor Spastic Dysphonia: Heterogeneity of Physiologic and Phonatory Characteristics
Pamela J. Davis, PhD; Daniel R. Boone, PhD; Raymond L. Carroll, FRACS; Paul Darveniza, MD, FRACP; Gordon A. Harrison, MB, BS 179

Abnormalities of Cilia in the Middle Ear in Chronic Otitis Media
Herman Yeger, PhD; Erma Minaker; David Charles, MD; Allen Rubin, MD, PhD; Jennifer M. Sturgess, PhD 186

Human Leukocyte Antigen-A, -B, -C Tissue Types in Patients With Middle Ear Cholesteatoma
Jens Ulrik Felding, MD; Christian Brahe Pedersen, MD; Lars U. Lamm, MD 192

Computerized Data Bank System for Temporal Bone Histopathology
Taeko Okuno, MD, DMS; Conrad Wall III, PhD; Isamu Sando, MD, DMS 195

Study of Toynbee Phenomenon by Combined Intranasopharyngeal and Tympanometric Measurements
Yehuda Finkelstein, MD; Yoav P. Talmi, MD; Yuval Zohar, MD; Nelu Laurian, MD 199

Immunologic Responses Against Lipopolysaccharide of *Hemophilus Influenzae* in Patients With Acute Sinusitis
Teruhiko Harada, MD; Yasuo Sakakura, MD 207

X-Ray Study of the Month. Orbital Cellulitis With Abscess Formation Caused by Sinusitis
Randall Clary, MD; Alfred L. Weber, MD; Roland Eavey, MD; Robert F. Oot, MD 211

Pathology Consultation. Surgical Margins in Squamous Cell Carcinomas
John G. Batsakis, MD 213

Letters to the Editor 215

Book Reviews 215

Instructions to Authors 218

Index to Advertisers 22a

PART 2

Workshop on Chronic Suppurative Otitis Media: Etiology and Management
Charles D. Bluestone, MD; Margaret A. Kenna, MD; Editors.
Mary D. Scheetz, MLS, Associate Editor . . . . Supplement 131

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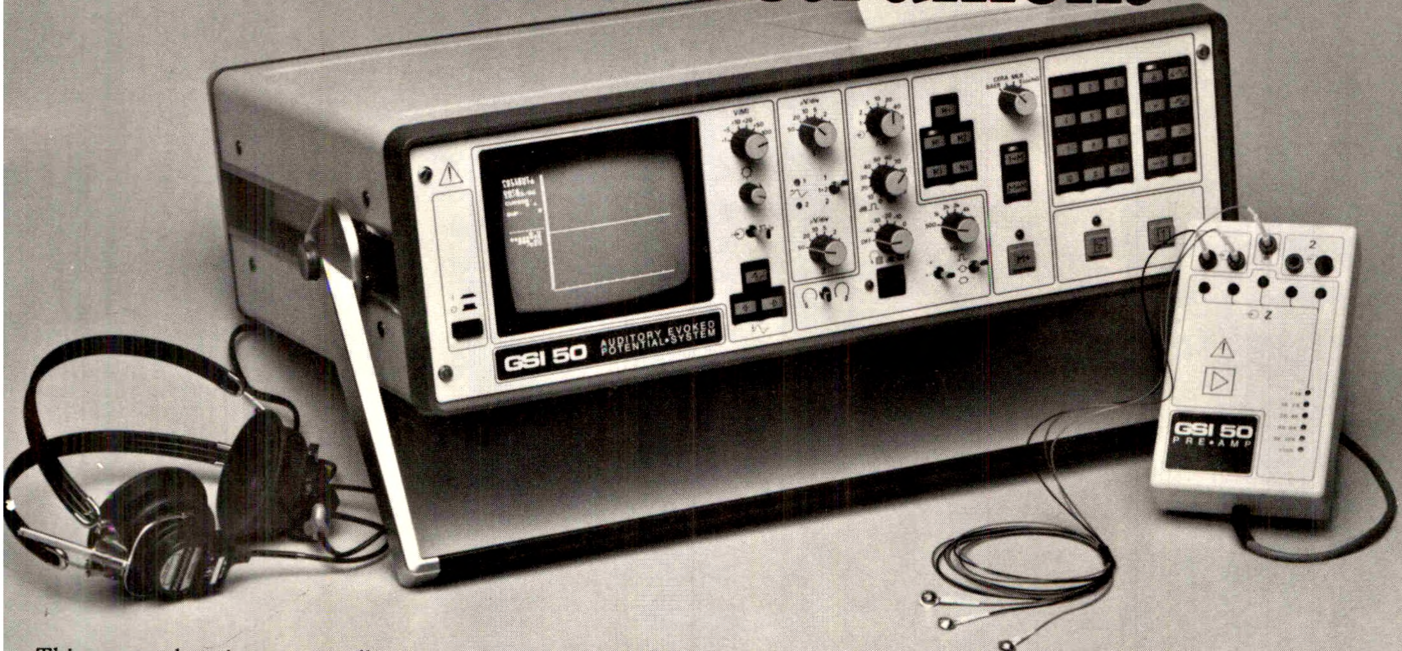

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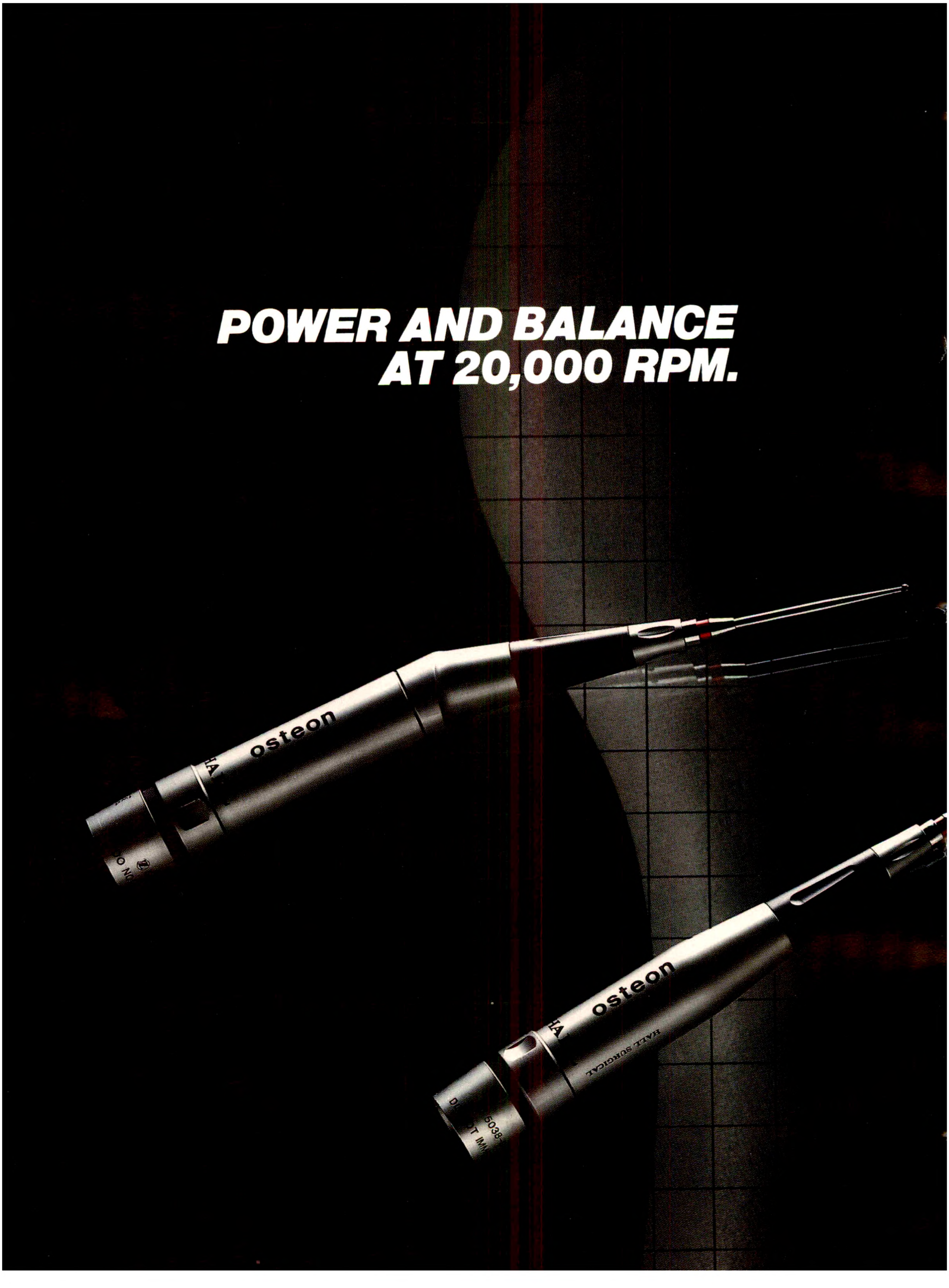
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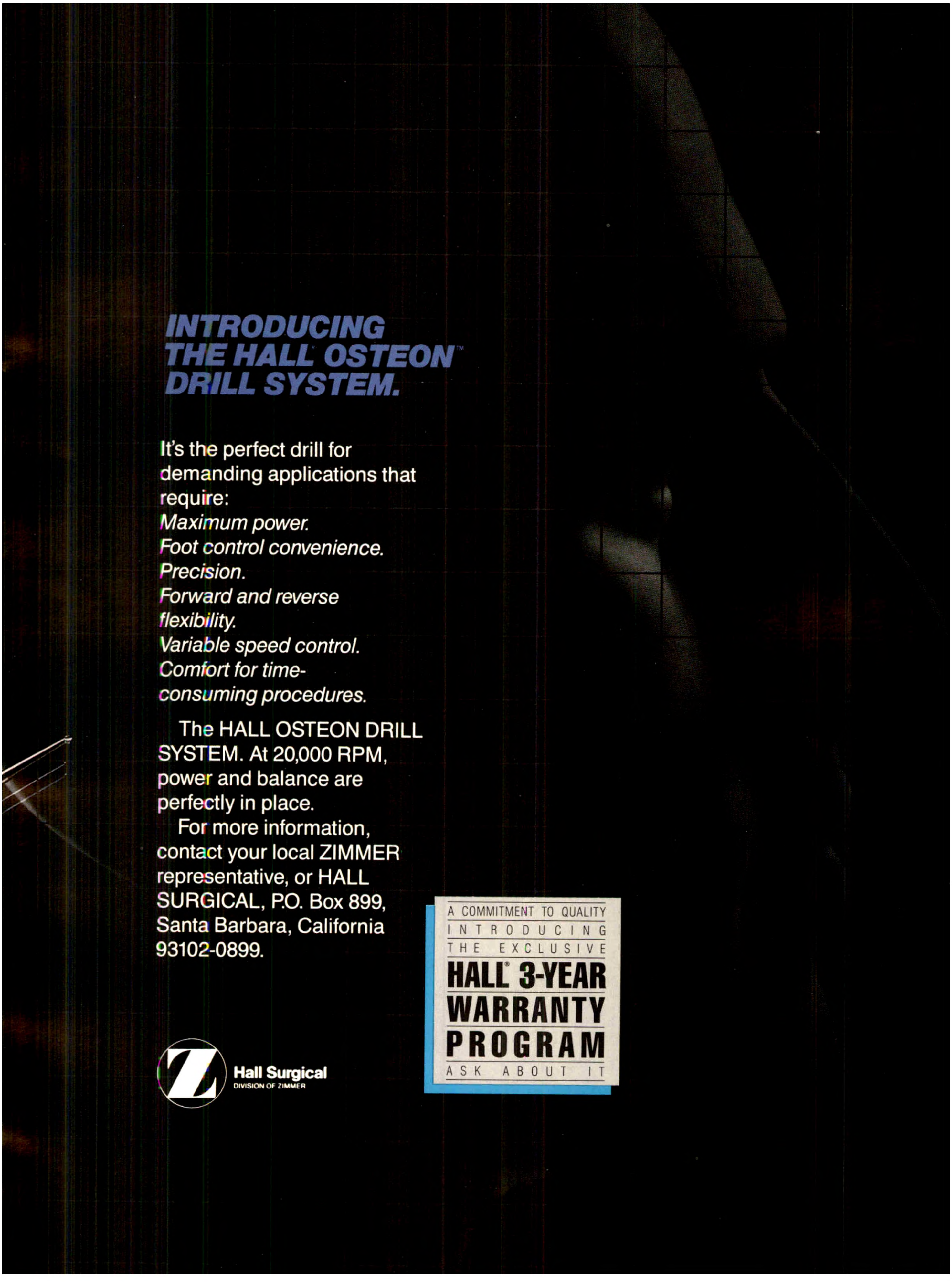

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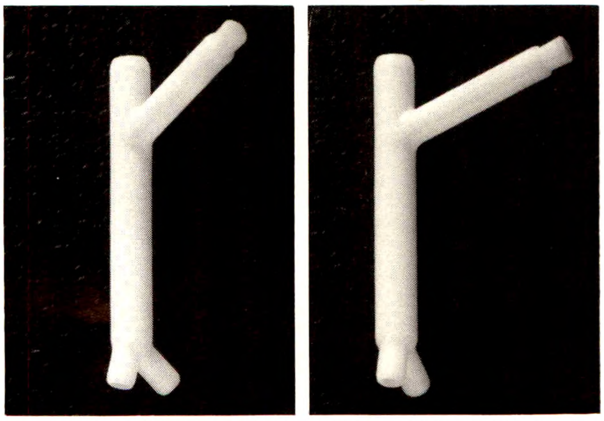

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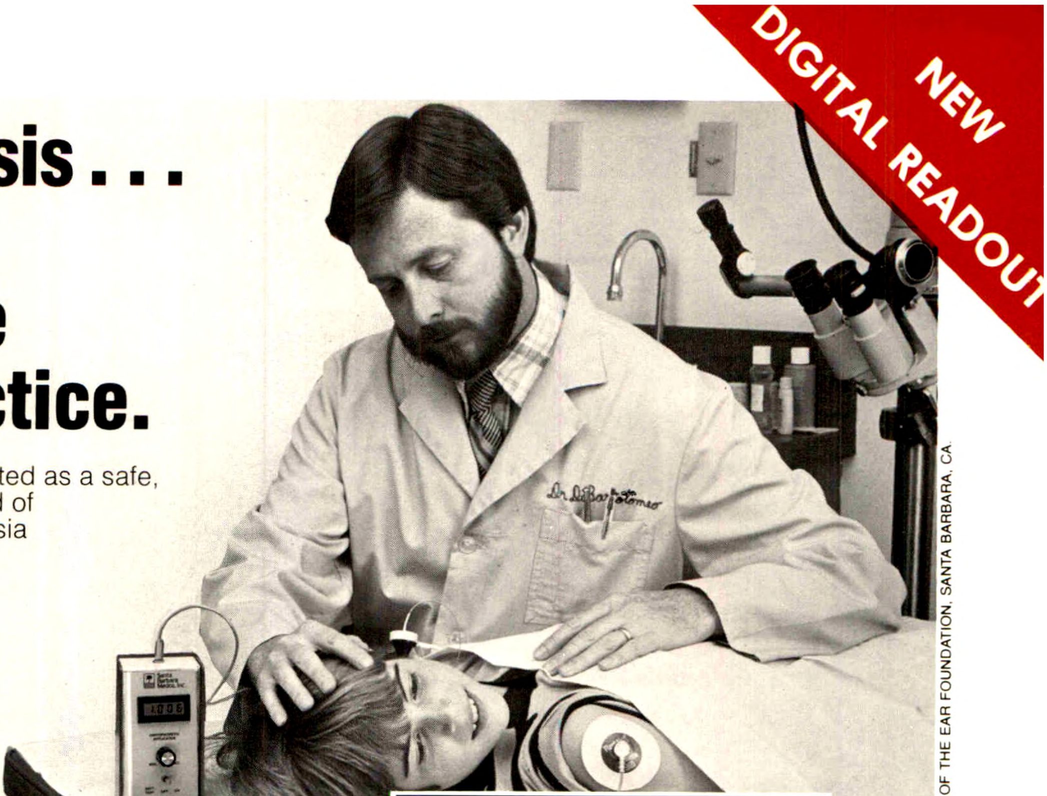

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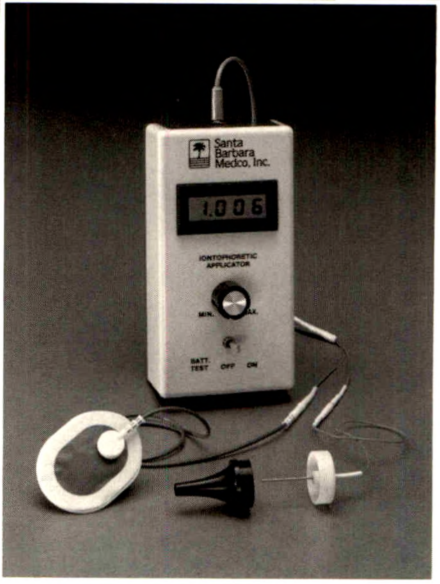

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1. Echols, D., Norris, and H. Tabb. "Anesthesia of the Ear by Iontophoresis of Lidocaine." Arch. Otolaryngology, 101, 1975, 418-421.
2. Comeau, M., and R. Brummett. "Anesthesia of the Human Tympanic Membrane by Iontophoresis of a Local Anesthetic." Laryngoscope, 88, 1978, 277-285.

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All alumni are invited to attend the scientific sessions on the mornings of Friday, September 23, and Saturday, September 24. A social program will be included. We are looking forward to this great event.

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A333

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PM 105 — RHINOPLASTY AND OTOPLASTY

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Fee: $750

Sidney S. Feuerstein, MD, Course Director; S. James Baum, MD, Saul Hoffman, MD, Willian Lawson, MD, DDS, Sigmund Sattenspiel, MD, and Guest Faculty: John Conley, MD, New York; Irvin Fine, MD, Perth Amboy, NJ; Alvin Glasgold, MD, New Brunswick, NJ; Frank Kamer, MD, Beverly Hills, Calif; Mark Krugman, MD, Tustin, Calif; Lionello Ponti, MD, Rome; Robert Simons, MD, Miami; Howard Smith, MD, DMD, New Haven, Conn; Richard C. Webster, MD, Melrose, Mass.

This course covers the basic principles of rhinoplasty including reconstructive surgery of the nasal septum and otoplasty. Basic lectures on surgery of the nasal tip will be thoroughly reviewed and discussed. Laboratory dissection on fresh cadavers will be coordinated with the lectures in addition to daily live and taped televised surgery. Anatomy, physiology, pathology, diagnosis, planning and evaluation in rhinoplasty will be thoroughly reviewed. Management of the nasal septum with and without rhinoplasty will be presented. Correction of nasal deformities including thorough discussion of component parts and their relation to every other part with special emphasis on the nasal tip and nostrils, splinting, correction of accompanying chin deformities, use of grafts for restoration of contour, plastic surgery in children, and psychiatric aspects will be reviewed. Management of nasal deformities associated with cleft palate and cleft lip will be presented.

The technique and latest concepts developed in rhinoplasty will be discussed and taught, including the prevention and correction of rhinoplasty sequelae. The importance of surgical judgment, proper association of the aesthetic and physiological requirements and methods of improvisation will be stressed.

Lectures on otoplasty will deal with etiology, pathology, and surgery of deformities of the auricle secondary to errors in shape, size, and position.

PM 167 — FACE-LIFT SURGERY

June 17-18, 1988
Friday and Saturday, 8 AM to 6 PM (Two Sessions)

Fee: $450

William Lawson, MD, DDS, Course Director; Sidney S. Feuerstein, MD, and Guest Faculty: John Conley, MD, New York; William H. Friedman, MD, St Louis; Frank M. Kamer, MD, Beverly Hills, Calif; Richard C. Webster, MD, Melrose, Mass.

This course will cover the face-lift procedure. It will include lectures on case selection, regional anatomy, operative technique, complications, and results. Attention will be given to ancillary procedures of the aging face. Fresh cadaver dissection and surgical demonstrations will be utilized.

Information: Director, The Page and William Black Post-Graduate School of Medicine, Mount Sinai School of Medicine, One Gustave L. Levy Place, New York, NY 10029; (212) 241-6737.

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Ann Otol Rhinol Laryngol 97:1988

PERILYMPH FISTULA: THE STANFORD EXPERIENCE

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Seventy-eight tympanotomies were performed to determine the presence of perilymph fistulas (PLFs); of these, 51% were found. The oval and round windows of all patients were grafted, whether PLFs were present or not. Of those patients with PLFs, 64% had resolution of their major symptom; when no PLF was found, 44% had a similar outcome. We concluded that 1) PLFs often behave as if they are epiphenomena in relation to hearing and balance, 2) PLFs can be intermittent, 3) PLF surgery is disappointing for restoration of hearing in sudden hearing loss when compared to the rate of spontaneous recovery, 4) stabilizing a fluctuating or progressive loss is a more realistic goal, and 5) establishing preoperative criteria for exploration is still a problem.

KEY WORDS — perilymph fistula.

INTRODUCTION

Many authors have tried to define the history, signs, and symptoms of perilymph fistulas (PLFs). The first PLFs were associated with previous stapes surgery,[1] with preceding head trauma,[2,3] and with a broader spectrum of events likely to have caused spinal fluid or abrupt middle ear pressure changes.[4] Subsequently, it was recognized that some PLFs were "spontaneous," without any historical marker.[5] Auditory symptoms included fluctuating hearing,[1,6] rapidly progressive and sudden hearing loss,[4,7] and no hearing loss.[8-11] The vestibular symptoms have included episodic vertigo with and without nausea and vomiting,[12,13] positional vertigo,[14] intermittent dysequilibrium,[11,13,15] and no balance symptoms.[4,11] It has been difficult to distinguish patients with Meniere's disease from those with PLF.

In brief, the literature on PLF seems at times conflicting and confusing. There are more than a few otolaryngologists who either are quietly skeptical that PLFs exist as clinical entities or believe that the numbers are exaggerated. Here we report both the positive and negative results for 65 patients, wherein no patient was said to have a PLF unless at least two competent observers agreed that a fistula was present. The results do little to clarify making the diagnosis of PLF. They do, however, suggest that PLFs are either epiphenomena of another disorder or have strong tendencies toward intermittence, frustrating any classic description.

METHODS

Sixty-six patients had explorations for PLFs between June 1974 and October 1985. Sixty-five records were available and were reviewed independently by both authors. These 65 patients are the subject of this report. The decision criteria to explore for PLF changed during this 11-year period, in response to both the published experience of others and the feedback of local accumulated experience. More explorations for hearing loss, often associated with "trauma," were done early on, while patients with spontaneous onsets of balance symptoms tended to dominate the more recent past. One author (F.B.S.) also became curious about the symptom similarities with Meniere's disease and explored several patients who had this diagnosis. Thus, in analyzing results, we looked specifically at the surgeon's goals, ie, curing a balance problem, a hearing problem, or both.

The patients' balance disturbances commonly consisted of postural unsteadiness, accentuated by physical activity of specific sorts: lying with the affected ear down, straining at stool, sneezing, or any other CSF pressure-changing event. Other patients had episodic vertigo, some with nausea and vomiting. Patients explored for hearing loss had either a sudden loss or a fluctuating loss with a progressive downward trend. Balance disturbances and hearing loss were usually both present in a given patient; however, the patient was explored primarily to treat one or the other.

Surgical selection was based primarily on history. Some patients presented with an event-related onset, such as head trauma, barometric pressure change, or a physiologic pressure change, such as Valsalva's maneuver. Other patients had no obvious precipitating factors, and the PLFs were termed spontaneous in onset.

An ear scored as positive for a PLF was verified by at least two observers, who both saw multiple reaccumulations of crystal clear fluid after multiple aspirations. The fluid was observed before any manipulation of the membranes or mucosa at the suspect window. We specifically excluded all "maybes" and "possibilities," including those patients in whom a change in the reflected light patterns changed with aspiration, but in whom no obvious fluid was actually seen. Early in the series,

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REPRINTS — F. Blair Simmons, MD, 300 Pasteur Dr, Rm R135, Stanford, CA 94305.

TABLE 1. OUTCOME AND NUMBERS OF PERILYMPH FISTULAS ACCORDING TO ONSET HISTORY

			Site			Cured/Improved	
Onset History	*No. Pts*	*PLF (%)*	*OW*	*RW*	*Both*	*PLF (%)*	*No PLF (%)*
Barometric pressure	7	57	0	3	1	100	0
Trauma	16	56	7	2	0	55	29
Valsalva's maneuver	6	66	4	0	0	75	50
Otologic surgery	3	33	1	0	0	100	50
Spontaneous	33	45	9	4	2	50	47
Totals						64	44

OW — oval window, RW — round window.

maneuvers to increase CSF pressure were tried in search of occult leaks, but none were found.

Nearly all operations were done under local anesthesia. It is important to note that both the oval and round windows were grafted, regardless of findings. Perichondrium was placed over instrument-excoriated mucous membranes. No bone was removed from the round window region. No additional middle ear packing was used, except on recurrences. No postoperative restrictions, except on activities known to cause CSF pressure changes, were ordered. Management was similar to that given to a patient with an uncomplicated stapedectomy.

Hearing results were judged from the audiogram obtained closest to the time of surgery and the most recent postoperative audiogram. Hearing was scored as "improved" if there was at least a 20-dB improvement in the 500- to 2,000-Hz average and if the hearing loss had been present for more than 30 days. A different "improved" criteria was used for patients operated upon subsequent to a sudden hearing loss who were still within the 30-day period in which some degree of spontaneous recovery could have been expected. In these few patients, "improved" was the increment given above, minus the average recovery expected if no exploration was done. These patients' improvements were therefore compared to the spontaneous recovery observed in patients with idiopathic sudden hearing loss.[7] Hearing loss was scored as "stabilized" when there was no further loss of hearing after the surgery.

Balance results were a scoring problem; "cured" and "no change" categories were clear enough, and those designations meant exactly what they said. There was a small in-between group who were better but still had minor degrees of spatial disorientation that no longer affected their life-styles. An example was the patient who had serious problems with true spinning vertigo who after surgery still had mild sensations of unsteadiness from time to time that were quite different from the preoperative problem. The descriptor "improved" was used for their outcome. Two patients were lost to significant follow-up and were counted in the "no change" group.

The sample of patients in this series probably does not reflect the community experience. Stanford is a tertiary care facility, which both benefits from and is subjugated by a highly intelligent "halo group" of community physicians who treat the classic PLF patient aggressively. Thus, very few post-stapedectomy or event-related onset PLFs have been referred here in recent years.

RESULTS

Two thirds of the 65 patients were female. The youngest was 2.5 years of age, and the oldest was 78 years of age (mean, 40 years). The numbers of left and right explorations were about equal, and both ears were explored in two patients. The average duration of symptoms was 4 years (range, 1 day to 28 years). Postexploration follow-up averaged 1 year (range, 1 week to 6 years). Fistulas were found in 33 (51%) and were more common in the oval than in the round window (21 versus nine), and three involved both windows. There were nine reexplorations, and two patients were operated upon three times.

Table 1 shows the historical onset events, number of patients for each, the percentage positive for PLF, and the percentage of cures according to the goals of each operation. The trauma category is troublesome, even though we tried to include only those patients in whom a blow to the head was a major event, such as a fracture, loss of consciousness, or injury requiring immediate medical attention afterward. Two onsets occurred within a year, and two patients developed symptoms more than 5 years after their injuries. These PLFs were categorized as traumatic in origin, despite the long delay in developing symptoms. The time relation for two patients could not be recovered from the records. Seven patients developed symptoms during external pressure changes, such as diving or altitude change. Six others had internal pressure changes, either Valsalvalike or from heavy physical exertion. One half of the patients experienced spontaneous

TABLE 2. CONFIGURATION OF THRESHOLD AUDIOGRAMS AND PREVALENCE OF PERILYMPH FISTULAS

Audiogram Slope	*No. Pts*	*PLF (%)*
Downward	32	56
Flat	6	50
Upward	5	60
Not classified	2	50
Normal hearing	20	50

TABLE 3. SPATIAL DISORIENTATION SYMPTOMS AND PREVALENCE OF PERILYMPH FISTULAS

Spatial Disorientation	*No. Pts*	*PLF (%)*	*Improved (%)*
Spinning, nausea/vomiting	19	58	63
Spinning	18	50	39
Postural unsteadiness	20	50	70

onsets; it is our recollection that many of these awoke in the morning with their symptoms present.

Hearing loss was the predominant symptom in 18 patients. Twelve patients experienced sudden onset, and seven had histories of hearing fluctuation. Table 2 shows the threshold contour of all the losses, according to previously published criteria.[7] This Table also illustrates one of the frustrations in dealing with PLF diagnosis: no "typical audiogram." There do seem to be two trends: down-sloping losses represent 50% of cases here but only 29% of cases with idiopathic sudden hearing loss. Further, no middle frequency-only losses appear, suggesting that such ears recover hearing without any help from the surgeon.

Vestibular dysfunction was the major symptom in 47 patients. Of these, the majority (78%) had episodic symptoms. In 60%, balance symptoms were worse, or only present with movement. The results shown in Table 3 suggest that the usual descriptors of a balance disturbance did little to distinguish PLFs or predict outcome.

Patients were not routinely examined by electronystagmography for positional nystagmus. However, 18 patients were found to have positional nystagmus on examination, ten of whom had PLFs at surgery. Electronystagmography was performed on 35 patients; of these, ten showed hypoactive calorics, and fistulas were found in eight.

We specifically reviewed records in search of characteristic head or body positions or movements that either aggravated or alleviated balance symptoms, and we failed to find anything convincing. For example, symptom increase with the affected ear down was used more than once as a determinate for which ear to explore for a PLF. Yet when that symptom was present, PLFs were found in 50%, the same rate as in the entire group. In spite of such data, it is still our clinical impression that this symptom is important in PLF syndromes.

Ten patients in the series had been diagnosed as having Meniere's disease by at least one otolaryngologist before exploration for PLFs. Such a diagnosis seemed reasonable in the majority of these patients, although these patients were not "classic." Seven PLFs were found and six of these had been cured. In the three normal ears that were grafted, one had a balance cure and another had both a significant hearing improvement and resolution of dysequilibrium. Follow-up on this subgroup has been longer than 2 years.

Fifty-five percent of the patients who had explorations had their symptoms cured or appreciably changed for the better; no patient's hearing or balance was worse after surgery. When a PLF was found, 64% had resolution of their major symptom. We should emphasize that 44% of patients in whom a PLF was not seen had similar outcomes as shown in Table 1. Of those who received grafts to stabilize a progressive hearing loss, 50% achieved that goal. However, only four patients had a 20-dB or better hearing improvement, and only two had an improvement beyond what might be expected without surgery.

DISCUSSION

Our results are impressively similar in many ways to the 51% positive incidence of PLF at exploration at the University of Iowa reported by Seltzer and McCabe.[13] The results are very different, both in incidence and cure rate, from the 93% vertigo cure rate of Healy et al,[3] and from the 86% incidence and 80% vertigo cure rate of Potter and Conner.[16] We certainly envy their cure rates, but each of these two studies has one possibly important procedural difference from ours.

Healy et al apparently followed Goodhill's advice about finding PLFs: ". . . at times it was necessary to use 25 and even 40 magnification to visualize the leak. In some patients 5 to 10 minutes elapsed before perilymph could be seen reappearing after carefully 'blotting' the footplate or round window regions . . . ."[3(p47),4] We would have missed this type of fistula or disagreed between the two observers. This did happen occasionally.

Potter and Conner took the advice of Daspit et al[illegible] and rarely explored for a PLF unless there was some form of positive fistula test or Hennebert's symptom. Had we done likewise, our incidence would have improved, but we would have missed 80% or more of the PLFs that we did find. A positive test is comforting when present, but is not a high-level decision criterion when it is negative.

It seems pointless to reiterate once again the frustration of many who have thought seriously about criteria by which to identify without surgery the patient with a PLF. Our impressions are much the same as those of Seltzer and McCabe, ie, that there is no classic constellation of histories and findings, only "flags which, when taken cumulatively in selective fashion, may be of help."[13] Singleton et al[14] chose the words "high index of suspicion" to imply much the same meaning.

The mimicking of Meniere's disease by PLFs probably encompasses the largest diagnostic problem of the patient population. Of the 17 papers reviewed in preparing this paper, and excluding isolated case reports, one half mention this as a diagnostic problem. The outcomes of our small series of ten cases should be taken seriously, although the patients did not have "classic" symptoms. We have observed that papers written about the diagnosis and management of Meniere's disease never mention a differential diagnosis from PLF. This paper must once again emphasize this overlap and perhaps suggest that weighing one of these two diagnoses over the other is often a self-fulfilling prophecy.

We are also faced here with a 64% cure rate for those who had a documented PLF, and a 44% cure rate for those having no PLF but who received grafts anyway. There is another tangential but pertinent statistic that needs to be included: a 17% repeat operation rate. Repeat explorations were done for two reasons. First, a PLF was found at the initial operation, but the patient's symptoms continued or recurred some time later, creating suspicion of a recurrent fistula. There were seven of these, and three did have a recurrence. In addition, repeat explorations were done when no PLF was found initially and there was a dramatic cessation of symptoms afterward, then recurrence. Perilymph fistulas were found in two of these ears, one 9 years after negative surgery.

In the larger series of one-time operations, it could be inferred that a sizable number of PLFs are indeed intermittent, and that this intermittence might account for no observed PLF, as well as known intermittence of some patients' symptoms. Second (and third) operations prove this occurs. The question really is, "how often?" This intermittence may also explain the improvement seen after treating ears in which no PLF was seen.

Another troublesome alternative is the presence of a very large placebo effect operating on the patient and surgeon that we are not willing to dismiss completely. This possibility is compounded by the inability to objectively document the operative disorder, as one can by submitting a diseased appendix for histopathologic confirmation.

Final consideration is given to those patients who did have a PLF, did not get better, and did not have a second operation. Some of these patients, whom we now know were unlikely to be cured in the first place, received grafts for sudden hearing losses. (Perilymph fistula surgery for stabilization of hearing is another matter not discussed here.) A number of patients operated upon for balance disorders as well did not get impressively better. The epitome of these was a patient with an obvious round window fistula who shortly afterward developed a classic case of Cogan's syndrome; we have not included her in this series. A number of authors have raised the possibility of a second problem, most commonly hydrops, being either concomitantly present or developing afterward, perhaps even as a result of the surgery. Clearly, if a PLF can be an epiphenomenon in hearing loss, there is no contradiction to the same assumption with balance mechanisms. Theory aside, the practical problem is gaining the wisdom to know when a repeat operation for a recurrent PLF is in order, or when it is time to move in other directions of therapy.

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Ann Otol Rhinol Laryngol 97:1988

STAPEDECTOMY TRENDS FOR THE RESIDENT

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HOUSTON, TEXAS

The diminishing number of cases of otosclerosis limits the training experience in stapes surgery during residency. Results are suboptimal. Closure of the preoperative air conduction to within 10 dB of bone conduction was obtained in only 64% of resident cases. Efforts to maximize experience and improve results include closer faculty supervision, use of one stapedectomy technique, and a prospective study of individual residents' performance.

KEY WORDS — otosclerosis, stapes surgery.

In 1952, Rosen[1] introduced stapes mobilization as treatment for conductive hearing loss due to otosclerosis. In proposing preliminary stapes palpation prior to the fenestration procedure in order to determine which cases should be operated, he demonstrated that palpation could loosen the footplate and restore hearing. In 1958, Shea[2] reintroduced footplate fenestration to reestablish mobility of the ossicular chain. His techniques replaced both fenestration and mobilization in the surgical management of otosclerosis. Since the evolution of stapedectomy in the 1950s, thousands of successful operations have been performed. The large volume of cases has produced refinements in techniques and prosthetic materials and has set standards for hearing results. Presently, however, there exists a general consensus that the pool of virgin otosclerotic ears is diminishing for both clinicians and residents in training. This depletion of cases is attributed to successful treatment by surgery and hearing aids, as well as to the increasing number of practicing otolaryngologists.

Limited experience in stapes surgery may jeopardize the potential successful outcome. Previously published reports of stapes surgery in training institutions reveal mixed results.[3-5] In an effort to examine our experience and to establish a strategy for resident training, a retrospective analysis of stapedectomies from 1975 to 1986 was performed. Additionally, a questionnaire assessing alumni experience and opinion was incorporated into the study to determine what the future of stapes surgery may hold for residents completing training.

MATERIALS AND METHODS

Two studies were undertaken as part of the evaluation of stapedectomy in a residency training program.

Baylor College of Medicine Alumni Survey. A stapedectomy questionnaire was forwarded to 110 alumni who had completed the residency program at the Department of Otorhinolaryngology and Communicative Sciences, Baylor College of Medicine, between 1950 and 1985. This questionnaire requested information on the number of stapedectomies performed as primary surgeon during residency, profile of clinical practice, continuing education experience in stapes surgery, techniques, and past and present experience in stapes surgery.

Retrospective Study. A review was made of all available complete records on poststapedectomy patients from 1975 to 1986. Surgery was performed by residents at the Baylor College of Medicine affiliated hospitals in Houston: The Methodist Hospital, Ben Taub General Hospital, and The Veterans Administration Medical Center. Only initial procedures for footplate fixation due to otosclerosis were reviewed. Exclusions included revision stapedectomies, congenital footplate fixation, stapes fixations due to tympanosclerosis, and cases of footplate extraction for traumatic fractures of the stapes arch.

Operative reports, discharge summaries, postoperative clinic notes, and preoperative and postoperative audiograms were reviewed. Data included sex, age, techniques, operative findings, hearing results, and complications.

An average of the preoperative air and bone conduction pure tone levels at 500, 1,000, and 2,000 Hz were compared to the best postoperative pure tone levels. The maximum score for the phonemically balanced word list (PBmax) was compared on preoperative and postoperative tests. Changes in bone conduction at 4,000 Hz were examined.

From the Department of Otorhinolaryngology and Communicative Sciences, Baylor College of Medicine, Houston.

Presented at the meeting of the American Otological Society, Inc, Palm Beach, Florida, May 3-4, 1986.

REPRINTS — Newton J. Coker, MD, Dept of Otorhinolaryngology and Communicative Sciences, Baylor College of Medicine, 1 Baylor Plaza, Houston, TX 77030.

TABLE 1. CRITERIA FOR REPORTING STAPEDECTOMY RESULTS

Result	*Criterion A* *(% Improvement)*	*Criterion B* *(Closure to Within 10 dB of Preoperative Bone Conduction)*	*Criterion C* *(Changes in Bone Conduction)*
Superior	≥ 100 (overclosure)	AC ≥ preoperative bone conduction	11 dB or better gain
Good	80-99	AC within 1-10 dB	No change or 1-10 dB gain
Fair	60-79	AC within 11-20 dB	1-10 dB drop
Poor	0-59	AC within 21-30 dB	11-20 dB drop
Failure	Loss	AC 31 dB or worse	20 dB or more drop

As proposed by Chandler and Rodriguez-Torro.[3]
AC — air conduction.

Calculations of hearing results were made according to the method suggested by Chandler and Rodriguez-Torro.[3] Their criteria for evaluating results are demonstrated in Table 1 and include 1) criterion A — percentage improvement or percentage closure of preoperative air-bone gap; 2) criterion B — closure to within 10 dB of preoperative bone conduction; and 3) criterion C — changes in bone conduction. All postoperative complications were tabulated.

RESULTS

Baylor College of Medicine Alumni Survey. Eighty-eight of 110 resident alumni (80%) returned the questionnaire. These clinicians are located predominantly in the southern half of the United States. The average practice profile is demonstrated in Fig 1 and reveals that 26.8% of clinical practice is devoted to otologic disorders. Of the respondents, approximately 25% felt that their experience in stapes surgery during residency was inadequate. Most of these resident alumni completed training in the last decade. Half of the resident alumni have attended stapes surgery courses since the completion of residency. Of 87 respondents, 32.2% no longer perform stapedectomies. Two of three have chosen a clinical practice in subspecialties other than otology.

Comparing stapedectomy to other otologic procedures, the alumni rated the degree of technical difficulty of stapedectomy or stapedotomy on a scale of one to ten, with one representing the easiest procedure, and ten the most difficult. The distribution of responses was skewed negatively, with a mean response of 6.5, a median of 7, and a mode of 8. Sixty-four percent of the resident alumni perform stapedectomies with complete or near-complete footplate removal followed by closure of the oval window with a tissue seal and Robinson prosthesis; 27% perform stapedectomies and use the Teflon wire prosthesis or House wire. Only 2% were performing stapedotomies.

The most interesting aspects of the survey were the trends that have developed during residency training and in clinical practice. A histogram demonstrates the number of stapedectomies performed by the resident alumni as primary surgeons during residency (Fig 2) and confirms the fact that fewer and fewer cases of otosclerosis are available for training purposes. The resident alumni also were asked to estimate the number of stapedectomies performed the first year in practice and for each 5-year interval thereafter. Tabulation of the cases performed by our resident alumni demonstrated that the number of stapedectomy procedures performed peaked in 1980 (Fig 3). The number of cases per resident alumni, however, has shown a steady decline as new otosclerotic cases have diminished and the number of physicians has increased. Forty percent of our alumni residents feel we now should limit the number of residents trained to perform stapes surgery because of this falling caseload for the otolaryngologist.

Retrospective Study of Stapedectomy Results. During the 10-year period from 1976 to 1985, 46 residents completed the training program at the Department of Otorhinolaryngology and Communicative Sciences and performed 125 stapedectomies as primary surgeon and assisted on 416 cases. The cases as primary surgeon per resident ranged from none to nine. Mean cases yearly per chief resident over the same decade ranged from 0.8 to 3.67. Most residents had only two or three cases as primary surgeon. Forty-seven complete records were available for review. Of these cases, 24 stapedectomies were performed on indigent patients and 23 on veterans. Patients who failed to return for postoperative evaluations and those with incomplete audiometric records were excluded from the study. The female to male ratio was 21:26 because of the influ-

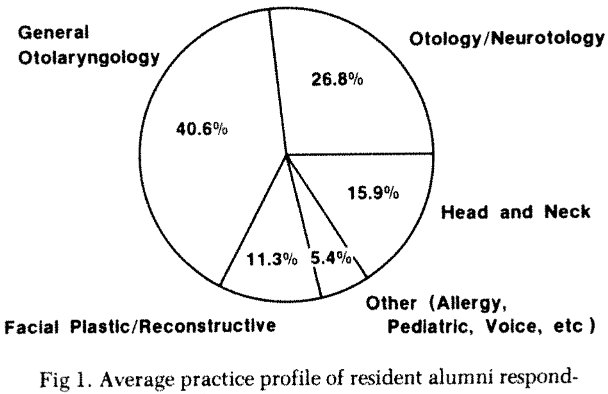

Fig 1. Average practice profile of resident alumni responding to questionnaire.

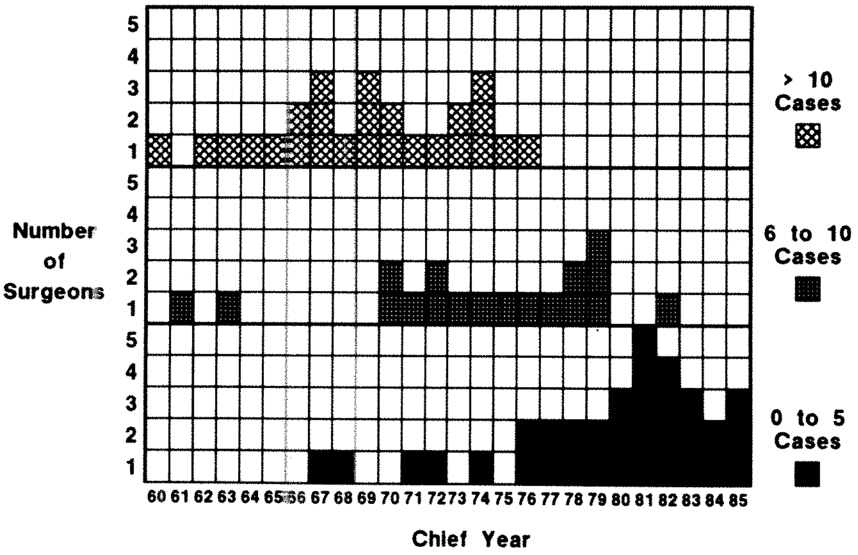

Fig 2. Stapedectomy procedures performed by survey respondents as primary surgeons during residency.

ence of the predominantly male veteran population. Stapedectomies in right ears outnumbered those in the left (26:21). Ages ranged from 10 to 64 years. Stapedectomy with tissue seal and Robinson prosthesis was performed in 75% of the cases. Stapedotomy with piston insertion comprised 15%. Other techniques were used in the remaining 10%. Results are outlined in Table 2. Superior or good results were achieved in 58% of cases, fair results were achieved in 17%, and in 25%, unsatisfactory improvement in hearing as defined by criterion A was achieved. Approximately two of three patients (64%) had overclosure or closure of the postoperative air conduction to within 10 dB of the preoperative bone conduction. Another 15% had closure to within 20 dB, but 21% of patients had poor outcomes or were operative failures. Changes in preoperative and postoperative bone conduction at 4,000 Hz were examined in 37 cases (Table 3). Ten cases were excluded because of concomitant severe sensorineural loss at 4,000 Hz, presumably secondary to cochlear otosclerosis, presbycusis, noise-induced damage, or other causes. Reliable measurements of the 4,000-Hz preoperative bone conduction in those cases were not feasible. Of the 37 cases, 29 (78%) demonstrated improvement, no change, or deterioration of less than 10 dB. Seven cases (19%) demonstrated an 11- to 20-dB deterioration of bone conduction at 4,000 Hz, and one patient had a 21- to 30-dB drop. Improvement or no change in the PBmax score occurred in 34 of 44 cases (77%) available for comparison (Table 4). Nine patients (20%) had a 1% to 10% deterioration in the PBmax score, and one patient (3%) had a greater than 10% deterioration. Complications occurred in 15% of cases. Three tears in the tympanic membrane occurred during surgery, but only one persisted as a perforation. One patient developed chronic positional dizziness and one a Tullio phenomenon. One postoperative perilymph fistula required conversion of a stapedotomy to stapedectomy with tissue seal. No cases of anacusis resulted, although one patient had postoperative air conduction thresholds higher than the preoperative levels.

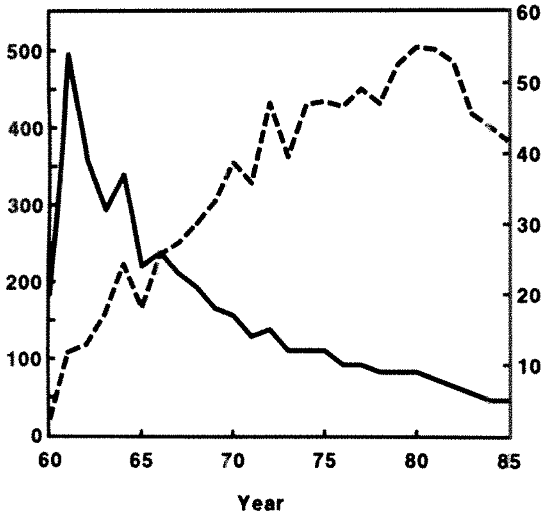

Fig 3. Stapedectomies performed by alumni following residency. Number of cases peaked in 1980. Average number of cases per physician per year has diminished to less than five. Broken line — stapedectomy procedures, solid line — stapedectomies per physician.

Forty-nine randomly chosen stapedectomy cases from the most experienced faculty member were reviewed. Superior or good results by percentage improvement in air-bone conduction gap were obtained in 40 of 49 cases (82%). Only four cases (8%) demonstrated poor results, and no failures oc-

TABLE 2. RESULTS OF STAPES SURGERY PERFORMED BY RESIDENTS, 1975-1986

	Improvement	*Closure of Preoperative Bone Conduction*	*Changes in Bone Conduction*
Superior	12 (26%)	13 (28%)	12 (26%)
Good	15 (32%)	17 (36%)	25 (53%)
Fair	8 (17%)	7 (15%)	9 (19%)
Poor	11 (23%)	4 (8%)	1 (2%)
Failure	1 (2%)	6 (13%)	0

TABLE 3. POSTSTAPEDECTOMY CHANGES IN BONE CONDUCTION AT 4,000 HERTZ

	Residents	Faculty Otologist
Less than 10 dB threshold elevation	29 (78%)	30 (77%)
11-20 dB deterioration	7 (19%)	6 (15%)
20 dB deterioration	1 (3%)	3 (8%)
Total	37	39

curred. Closure to within 10 dB of preoperative bone conduction was obtained in 88% of cases. There were no significant changes in bone conduction in the speech frequencies, but examination of changes in bone conduction at 4,000 Hz revealed improvement, no change, or less than a 10-dB deterioration in 30 of 39 cases (77%). An 11- to 20-dB threshold drop occurred in six cases (15%). Deterioration of more than 20 dB occurred in three cases (8%), but this number is statistically insignificant because of the limited number of patients in the overall study. The depression of the $\text{PB}_{\max}$ score for the staff otologist reflects the results of audiograms in the early postoperative period, ie, less than 1 month poststapedectomy. Two cases had transient postoperative positional dizziness, but no other complicating problems occurred. A comparison of results is summarized in Tables 3 through 5.

DISCUSSION

Results of the resident alumni survey clearly indicate that not only are the number of otosclerosis cases available for surgery diminishing in the training institution, but they are also declining in the otolaryngology practice at large. The dissatisfaction with stapes surgery during training over the past decade and the large percentage of alumni (40%) who feel we should limit the number of residents trained to perform stapedectomies highlight the dilemma of limited numbers and experience. It is unlikely that one can train all residents and expect them to maintain skills with less than five cases per year. Fortunately, many of the resident alumni have realized the shortcomings of inexperience and have elected not to perform stapedectomies. Although the majority of these individuals are subspecialists in areas outside otology, many have chosen to refer cases to more experienced partners or colleagues. This self-selection process for limiting the number of active stapes surgeons should be encouraged at the residency level. Those residents deciding to pursue nonotologic subspecialties need to relinquish cases to the other residents in order to enhance their stapes surgery training experience. The alternative is not to train residents, in part or altogether. With such limited numbers, why should stapedectomy be any different from other relatively uncommon otologic procedures, eg, facial nerve decompressions medial to the geniculate ganglion, vestibular nerve sections, or endolymphatic sac operations?

TABLE 4. POSTSTAPEDECTOMY CHANGES IN MAXIMUM SCORE FOR PHONETICALLY BALANCED WORD LIST

	Residents	Faculty Otologist
No change or improved	34 (77%)	26 (58%)
1% to 10% deterioration	9 (20%)	11 (24%)
10% deterioration	1 (3%)	8 (18%)
Total	44	45

The results of residents' stapes surgery at our institution are comparable to those reported by Chandler and Rodriguez-Torro.[3] Closure of the postoperative air conduction to within 10 dB of the preoperative was achieved in 62% of their resident cases, as compared to 64% in ours. Unsatisfactory results were 38% and 36%, respectively. Their average number of procedures per residents was seven, and ours, less than three. In Israel, where the otosclerotic pool is less depleted, Shapira et al[5] noted that residents achieved satisfactory results in 79% of cases and felt that the good results were in large part due to the availability of cases, approximately 18 per resident. Furthermore, their satisfactory results in the first 2 years of residency — 70% — were considerably inferior to those during the following year and a half of training (89%). The findings underscore the importance of experience in acquiring successful stapedectomy results. In the evaluation of 44 consecutive stapedectomies performed by 20 senior residents, Engel and Schindler[4] reported closure to within 10 dB of the preoperative bone conduction in 75% of cases. They believe that successful stapes surgery can be achieved in residency programs in spite of limited numbers, provided residents have other adequate otologic experience including temporal bone courses, learn a consistent and reliable technique, and operate under close faculty supervision.

Self-examination of the stapes surgery experience is incumbent on every training institution. Our results are comparable to those of other departments, but need to be improved to acceptable standards, ie, closure of air conduction to within 10 dB of preoperative bone conduction in at least 85% to 90% of cases. Present measures to improve results include supervision of all cases by faculty members with extensive otologic experience. Emphasis has been placed upon learning one technique well. The stapedotomy technique has been abandoned, except for obliterative cases. In our experience, this technique is more difficult to master than footplate ex-

TABLE 5. STAPEDECTOMY RESULTS, RESIDENTS (VERSUS FACULTY OTOLOGIST)

	Percentage Closure of Preoperative Air-Bone Gap	Closure to Within 10 dB of Preoperative Bone Conduction
Superior or good	58% (82%)	64% (88%)
Fair, poor, or failure	42% (18%)	36% (12%)

traction and insertion of a Robinson prosthesis over a vein or perichondrium graft seal. A prospective study as advocated by Chandler and Rodriguez-Torro[3] has been undertaken in an effort to identify problem residents in order that corrective measures can be instituted to maximize a limited experience. Such measures include additional time in the temporal bone laboratory and postponement of stapes surgery until additional experience in middle ear and mastoid surgery has been accumulated. Failure to train residents competent in stapedectomy technique because of a limited number of cases will result ultimately in stapes surgery's becoming a subspecialty experience.

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AIRWAY MANAGEMENT OF ACUTE SUPRAGLOTTITIS AT THE CHILDREN'S HOSPITAL, BOSTON: 1980-1985

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A controversy has existed in recent years regarding the ideal method of establishing and maintaining an airway in the pediatric patient with acute supraglottitis. Nasotracheal intubation has been used as the sole method of airway management of acute supraglottitis at The Children's Hospital, Boston, since 1970. This paper reviews our experience with 80 children with acute supraglottitis presenting at our institution during the years 1980 to 1985.

KEY WORDS — acute supraglottitis, airway management, epiglottitis.

INTRODUCTION

During the past 15 years, the method of establishing and maintaining an airway in the pediatric patient with acute supraglottitis has evolved gradually from tracheotomy to a preference for nasotracheal intubation. Several recently reported series have demonstrated the efficacy and relative safety of nasotracheal intubation.[1-5] The method avoids an operative procedure, and morbidity is equal to or less than that for tracheotomy.

Nasotracheal intubation has been used as the sole method of airway management of acute supraglottitis at The Children's Hospital, Boston, since 1970. We reviewed our experience over the past 5 years so that we might compare our results, including immediate and delayed complications, with results achieved in other reported series.

As the acute inflammatory process may involve all or part of the supraglottic structures, we prefer the term supraglottitis rather than epiglottitis. Occasionally, cases have been observed in which the inflammation involves the arytenoid mounds, aryepiglottic folds, and false vocal cords, with minimal involvement of the epiglottis.

PATIENTS AND METHODS

We reviewed the hospital records of all patients admitted to The Children's Hospital, Boston, with a diagnosis of acute supraglottitis between April 1, 1980, and March 31, 1985. This consisted of 80 patients (Table 1). Fifty-one patients were managed solely at our institution, and 29 patients underwent establishment of an airway via nasotracheal intubation at outside community hospitals and were subsequently transferred to our institution for further care.

Each patient's hospital chart was reviewed and data concerning immediate and long-term complications tabulated. An attempt was made to contact the parents of the children by telephone and question them in detail concerning any significant history of stridor, recurrent croup, or upper respiratory infection, exercise intolerance, or any other symptoms that might indicate clinically significant upper airway disease. We were able to contact the parents of 30 children. The length of follow-up ranged from 2 months to 5 years (mean, 2.3 years).

MANAGEMENT PROTOCOL

Children seen at The Children's Hospital, Boston, with a suspected diagnosis of acute supraglottitis are handled in the following manner.

Emergency Room. If our institution is notified that a child with suspected acute supraglottitis is en route, the otolaryngologist and anesthesiologist on call are notified and are present when the child arrives in the emergency room. A rapid but detailed history is obtained. Examination is kept at a minimum and confined to visual inspection and auscultation of the heart and lungs. Once the diagnosis is strongly suspected, the supraglottitis protocol is instituted. Excessive manipulation by physicians, nurses, and emergency room personnel is avoided. The child is allowed to sit upright in the company of the parents. No intravenous lines, hematologic studies, or blood gas studies are undertaken in an effort to keep manipulation to a minimum in the acute stage. If the patient is not in extreme circumstances, he or she is taken to the radiology department for a single lateral soft tissue radiograph of the neck. This may be helpful in confirming the diagnosis in cases that are not clear-cut; however, an x-ray study should never replace strong clinical suspicion and should

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TABLE 1. METHOD OF AIRWAY MANAGEMENT IN 80 PATIENTS

Method	Children's Hospital (N = 51)	Boston Area Community Hospitals (N = 29)
Operating room intubation	47	24
Emergency room intubation	2	5
No intubation	2	0

TABLE 2. EMERGENCY ROOM INTUBATIONS IN SEVEN PATIENTS

Location	Intubation and Anesthetic Techniques	
Children's Hospital	Diazepam and succinylcholine	1
	No anesthetic	1
Total		2/51
Boston area community hospitals	Diazepam and succinylcholine	3
	No anesthetic	1
	Cricothyroid puncture, intubated	1
Total		5/29

never be attempted in a child in extreme distress. Gentle oxygen assistance by mask is given as the child is transported to the operating room in the arms of his parents, accompanied by the attending pediatrician, anesthesiologist, and otolaryngologist.

Operating Room. Upon arrival in the operating room, the anesthesiologist begins mask inhalation anesthesia with the child sitting upright in the parent's lap. Meanwhile, the otolaryngologist readies the proper size laryngoscopes, bronchoscopes, and accessory equipment. A tracheotomy tray is opened. Masks are not worn by operating room personnel to avoid frightening the child.

The anesthesiologist accomplishes anesthetic induction using 2% or 3% halothane with oxygen delivered by mask. Nitrous oxide is avoided so as not to decrease oxygenation. When the child begins to relax, he is placed in a supine position and inhalation anesthesia is continued with a tight-fitting mask, using adequate positive pressure to overcome the supraglottic obstruction. Because of this obstruction, the induction period is usually prolonged and may last up to 10 minutes. Manipulation of the patient's airway should not be undertaken until a satisfactory plane of anesthesia is reached. Premature laryngoscopy may precipitate laryngospasm and severely complicate the procedure. Once an appropriate level of anesthesia is reached, an intravenous line is started and atropine given to block the vagal response. Preparations are then made for orotracheal intubation. The anesthesiologist and otolaryngologist visualize the larynx and confirm the diagnosis of supraglottitis. The anesthesiologist then passes an endotracheal tube (soft polyvinylchloride and cuffless) that is generally one size smaller than would be used for an elective case in the particular child. After the oral tube is in place, the otolaryngologist inspects the larynx and obtains a swab for culture. Under direct vision, the orotracheal tube is then changed to a nasotracheal tube and secured to the nose.

Blood cultures are then taken and intravenous ampicillin (200 mg/kg/day q 4 h) and chloramphenicol (100 mg/kg/day q 6 h) are administered. The infecting organism in the majority of cases is *Hemophilus influenzae* type b. The chloramphenicol is discontinued if subsequent blood cultures reveal sensitivity to ampicillin.

Intensive Care Unit. The patient is taken to the intensive care unit (ICU), where he or she is sedated with chloral hydrate and placed in a humidified tent. Hand restraints are fashioned. An effort is made to avoid attaching any accessory equipment to the nasotracheal tube to avoid accidental extubation. Intubation is maintained for 36 to 60 hours. Approximately 36 hours postintubation, positive pressure is applied to the endotracheal tube and leakage of air from around the tube determined by an audible air leak. If an air leak at less than 20 to 30 cm of water around the tube is demonstrated, the patient is extubated. If an air leak is not demonstrated at less than 20 to 30 cm of water around the tube, then the endotracheal tube is maintained in position and the air leak determination is repeated in 6 to 12 hours. When a sufficient air leak is demonstrated, the patient is extubated. In general, extubation is performed during the early morning hours to late afternoon and avoided at night. In earlier years, we performed direct or flexible fiberoptic laryngoscopy at the bedside to check the status of the supraglottic inflammation. As the determination of an air leak has proven to be a reliable indicator of the extent of laryngeal inflammation in recent years, direct visualization of the larynx has not been necessary.

Hospital Ward. Following extubation, the patient is observed in the ICU for 4 to 6 hours and transferred to the ward if all is well. Intravenous antibiotics are continued for an additional 5 days, for a total of approximately 7 days. The patient is discharged and oral antibiotics are continued for an additional 2 weeks. Siblings are treated with prophylactic rifampin for 4 days following the patient's arrival at home.

Community Hospitals. With few exceptions, children with acute supraglottitis seen first at Boston area community hospitals are managed initially as has been outlined above. Once an airway has been established by nasotracheal intubation and the patient stabilized, our institution is notified. A transport team consisting of an ICU nurse and pediatric resident is dispatched to the community hospital. The patient is then brought to our institution for the remainder of care.

RESULTS

Initial Intubation and Anesthetic Technique. Five patients presenting with acute supraglottitis to community hospitals and two patients presenting at our

TABLE 3. OPERATING ROOM INTUBATION AND ANESTHETIC TECHNIQUES

Technique	*Children's Hospital (N = 47)*	*Boston Area Community Hospitals (N = 24)*
Halothane and oxygen	42	18
Ketamine, halothane, oxygen	5	0
Diazepam and succinylcholine, oxygen	0	1
No anesthesia	0	0
Data unavailable	0	5

institution experienced respiratory and cardiac arrest within several minutes before or after arrival in the emergency room (Table 2). All patients were intubated successfully in an emergency situation. One patient at an outside hospital underwent cricothyroid puncture with a large bore catheter followed by oral intubation. Of the two patients presenting at our institution, one suffered a respiratory arrest while in an automobile 2 minutes from the hospital. He was orally intubated without anesthesia immediately upon arrival. The second child experienced a generalized seizure and subsequent respiratory arrest shortly after arrival in the emergency room. Following administration of diazepam and succinylcholine, he was orally intubated. Both patients were taken to the operating room for examination under anesthesia and replacement of the orotracheal tube with a nasotracheal tube.

Two patients were managed medically at our institution without establishment of an artificial airway. In both cases the diagnosis of acute supraglottitis was missed initially. The first patient was a 3-year-old girl who presented with a 36-hour history of sore throat, generalized malaise, and decreased oral intake. Physical examination revealed mild pharyngitis and meningismus. She was febrile (40° C), with a normal respiratory rate and no stridor. Laboratory studies revealed a moderately elevated WBC count and ESR. Chest and lateral neck radiographs were read as normal. Examination of the CSF, which included Gram's stain, was unremarkable. The patient was sent home with a diagnosis of generalized viral syndrome. According to the parents, she spent a relatively restless night at home with periods of noisy breathing, but was improved the next morning. The lateral neck x-ray study performed the previous night was reviewed and felt to be consistent with supraglottitis. The parents were contacted and asked to return the child to the hospital. Upon arrival, she had mild nasal flaring, but no stridor. She was breathing comfortably and seemed improved from the previous night. Because of the noticeable improvement, it was elected to treat her medically. Intravenous ampicillin and chloramphenicol were administered and the patient was admitted to the ICU. A repeat lateral neck radiograph was again consistent with supraglottitis. Blood cultures subsequently yielded *H influenzae* type b sensitive to ampicillin. The patient improved rapidly and was discharged on the fifth hospital day. The second patient presented in a similar manner (diagnosis made the following day after review of the lateral neck radiograph) and was managed successfully with airway observation and intravenous antibiotics.

TABLE 4. REASONS FOR UNPLANNED EXTUBATIONS IN TEN PATIENTS

Self-extubated in ICU and reintubated	6
Self-extubated in transport to Children's Hospital and reintubated	1
Tube changed electively, plugged (in ICU)	1
Tube changed electively, too small (in ICU)	1
Oral tube changed to nasal tube upon arrival at Children's Hospital	1

In the majority of cases, the patients were taken to the operating room and nasotracheal intubation was accomplished in an orderly fashion (Table 3). These patients included 47 children managed at our institution and 24 children managed at Boston area community hospitals. Specific data concerning the anesthetic agent used were not available for five operating room intubations performed at the community hospitals. Most of the children were managed with halothane and oxygen induction as described in detail above. On one occasion, a diazepam and succinylcholine combination was used. At our institution, ketamine was used on five occasions in uncooperative older children who would not accept a mask. Intramuscular ketamine was always followed with the halothane and oxygen inhalation technique.

All operating room intubations were performed without difficulty at our institution and at the community hospitals. One patient had his tube inadvertently dislodged by the otolaryngologist during inspection of the larynx. The tube was replaced without difficulty.

Course of Intubation and Hospitalization. The average period of intubation for the 80 patients was 2.2 days, and the average length of hospitalization was 7.5 days. Problems encountered with endotracheal tubes are listed in Table 4. Six children managed to extubate themselves within 48 hours of the initial intubation. In all cases, the tubes were replaced without difficulty. This was accomplished with intravenous diazepam and succinylcholine, or halothane and oxygen inhalation, usually within 10 minutes of extubation. One patient was reintubated following extubation in the ambulance while en route to our institution. No patient who experienced self-extubation was observed and not reintubated, even if approaching 36 hours in the ICU. Two tubes were changed electively: one because of plugging with mucus and another because the initial tube was too small. A third patient had the oral tube changed to a nasotracheal tube following arrival at our institution. Tube changes in all ten instances were accomplished without difficulty.

Of the 78 patients who were intubated, none required reintubation for airway obstruction following planned extubation at 36 to 60 hours.

Immediate Complications. All immediate complications, including the incidence of extraepiglottic infection, were reviewed (Table 5). Particular attention was paid to pulmonary complications. Atelectasis, pneumonia, pulmonary edema, and pleural effusion were differentiated based on typical findings on chest radiographs. In all cases, the pulmonary problems responded to physiotherapy, brief positive pressure ventilation, and diuretics, and eventually resolved without sequelae. Hospitalization was prolonged from 3 to 5 days in those patients with pneumonia, pleural effusion, or pulmonary edema. A single case of mild pericardial effusion resolved completely. Septic complications included one case of periarticular cellulitis of the ankle and one case of periorbital cellulitis. Both infections eventually resolved. One child had bleeding from the nasal cavity following placement of the nasotracheal tube. This persisted as a slow ooze for the next 18 hours and finally resolved. Hematologic studies revealed a prolonged prothrombin time that normalized prior to discharge. One patient was intubated without incident for supraglottitis, but developed meningitis and had a rapid downhill course resulting in death. Meningitis is an uncommon complication of acute supraglottitis, and was responsible for the single death in our group of patients.[6]

Otitis media, exudative pharyngitis or tonsillitis, and cervical lymphadenopathy have been included in published series concerning the incidence of extraepiglottic infection in acute supraglottitis.[7,8] Because hospital records were occasionally incomplete concerning these manifestations, we were unable to tabulate exact numbers. By our best estimate, these problems occurred in less than 20% of the patients.

Delayed Complications. For all 80 patients in this series, review of the hospital records failed to reveal any subsequent admissions for any complaint related to upper airway obstruction following the original admission for supraglottitis. The parents of 30 children (38%) were contacted. In all cases, the children were well and healthy without any symptoms that might indicate clinically significant upper airway disease.

DISCUSSION

There is no doubt that a debate concerning the ideal method of airway management in acute supraglottitis in children has been raging for the past 15 years.[1,9] Methods have included 1) tracheotomy, 2) nasotracheal intubation, and 3) selective medical management with no artificial airway. Disagreement has been lessened somewhat in recent years, as most physicians who diagnose and treat this problem prefer nasotracheal intubation. Proponents of tracheotomy[10,11] cite the following.

TABLE 5. IMMEDIATE COMPLICATIONS AND INCIDENCE OF EXTRAEPIGLOTTIC INFECTION IN 80 PATIENTS

Complication	*No. Patients*
Pulmonary	
Atelectasis	4
Pneumonia	5
Pleural effusion	1
Edema	2
Pericardial effusion	1
Periarticular cellulitis	1
Periorbital cellulitis	1
Epistaxis from nasotracheal tube	1
Meningitis/death	1
Otitis media	<20%
Pharyngitis/tonsillitis (exudative)	<20%
Cervical lymphadenopathy	<20%

1. It is a time-honored, relatively safe, and dependable method of ensuring the airway in this life-threatening disease.
2. It bypasses the disease, therefore the potential for added trauma to the airway with subsequent scarring and stenosis is minimal.
3. Performed properly, it results in complication rates equal to or lower than those for nasotracheal intubation.
4. Problems with endotracheal tubes are avoided, namely, endotracheal tubes are more easily dislodged and plug faster, thereby requiring more sophisticated nursing skills and intensive care facilities.
5. Tracheotomy tubes are easier to manage in the community hospital setting.
6. It is easier to find surgeons experienced in bronchoscopy and tracheotomy than it is to find anesthesiologists experienced in endotracheal intubation of pediatric inflammatory airway disease.

Those physicians favoring nasotracheal intubation[1-5] over tracheotomy state the following reasons.

1. Nasotracheal intubation avoids an operative procedure.
2. Published series report decreased mortality and complication rates equal to or lower than those for tracheotomy.
3. There is decreased hospitalization.
4. If accidental extubation should occur, the airway is maintained for 30 to 60 minutes because of the stenting effect of the endotracheal tube, whereas accidental decannulation of a tracheotomy tube could be disastrous.
5. As the method has gained popularity, increased numbers of anesthesiologists and otolaryngologists are becoming proficient with the technique.

Some authors[12] advocate selective initial medical management, with administration of intravenous antibiotics and corticosteroids and careful observation of the airway. Positive pressure ventilation by bag and mask is used to support ventilation as needed. This method should be given an initial trial of several hours with the physician in constant attendance, and only in children with minimal upper airway obstruction. If symptoms do not improve, or cyanosis or exhaustion develops, then establishment of an artificial airway should be undertaken.

During the early 1970s, as nasotracheal intubation began to replace tracheotomy, it was stated that nasotracheal intubation should only be used at major medical centers in which three elements were available: 1) expert pediatric anesthesiology, 2) expert pediatric otolaryngology, and 3) nursing and ICU personnel skilled in the management of pediatric airway problems. However, as greater numbers of pediatricians, anesthesiologists, otolaryngologists, and pediatric nurses have become familiar with the technique and maintenance of nasotracheal intubation, the method is being employed relatively safely with greater frequency in community hospitals.[5]

Our results indicate that the method of nasotracheal intubation is being used with good success in the greater Boston area. Excluding patients intubated in the emergency room, our review of hospital records indicates successful intubations without significant difficulty in 47 patients handled initially at our institution and 24 patients intubated in the operating room at Boston area community hospitals. There were no cases requiring emergency bronchoscopy or tracheotomy. Once intubated, problems encountered with tubes were small in number and quickly rectified. Accidental extubations occurred in seven patients (7 of 78 or 9%). This number compares favorably with the percentages of accidental extubations reported by DiTirro et al (9%),[5] Bottenfield et al (16%),[4] and Schloss et al (5%).[1] The average length of hospital stay (7.5 days) and the average time of intubation (2.2 days) are both well within the range reported by most large series in the literature.[1-5,13] The incidence of extraepiglottic infection and immediate complications in our series is comparable to that reported in other series.[1-8,13] No evidence of short-term or long-term upper airway disease secondary to endotracheal intubation could be detected by chart review and contact of at least one third of the patients treated. We note that our method of long-term follow-up is highly subjective; however, if a parent states that a child is well and without significant upper airway symptoms, then the chance that any significant laryngeal or tracheal disease exists is small. The anesthetic methods available for direct laryngoscopy and tracheal intubation in acute supraglottitis have been reviewed and include inhalational, intravenous, and mixed (inhalational and intravenous) techniques.[14] Some institutions perform intubations without anesthetic, using either a bronchoscope or endotracheal tube with the child fully conscious breathing 100% oxygen by mask.[11,15] The anesthesiologists at our institution prefer inhalational induction as has been described in detail above. A halothane and oxygen combination is used most often. Muscle relaxants are avoided. A very real problem that is seldom mentioned in papers discussing the management of acute supraglottitis is what to do with the older child who absolutely refuses to have a mask placed on the face. Our protocol for this problem is to give a single intramuscular dose of ketamine followed by halothane and oxygen. The use of ketamine has been criticized by some as it may potentiate laryngospasm.[16] This was not a problem in the five patients given ketamine at our institution. This may be due to the fact that halothane and oxygen inhalation is always administered following the ketamine to be certain that a correct plane of anesthesia is reached prior to intubation.

We believe the airway should be given absolute priority in this disease. Unlike laryngotracheobronchitis, it is difficult to assess the degree of obstruction in acute supraglottitis. Because complete airway obstruction may occur rapidly and without warning, patients with suspected supraglottitis should have an examination under anesthesia and an artificial airway in the form of a nasotracheal tube placed. For this reason, airway observation with bag and mask ventilation, corticosteroids, and racemic epinephrine are not a part of our protocol in the management of this disease.

The experience and facilities available for the care of acute supraglottitis may differ among institutions. The most important therapeutic aspect concerning this disease is the establishment and maintenance of an airway.[17] Nasotracheal intubation, when performed by expert pediatric anesthesiologists and otolaryngologists and maintained by expert pediatric ICU physicians and nurses, is a relatively safe and successful method of airway management in acute supraglottitis. If any of these elements is lacking, then time-honored tracheotomy should be the method of choice. Each local institution should establish a uniform policy for the management of supraglottitis based on its results. This avoids controversies regarding treatment that might waste precious time in caring for the acutely ill child.

CONCLUSION

The method of airway management of acute supraglottitis in children at our institution and Boston area community hospitals has been reviewed. Examining our results of the past 5 years, we believe the method is working successfully. We therefore plan to continue our management protocol for acute supraglottitis as it is currently practiced.

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UNIVERSITY OF CAPE TOWN, POSTGRADUATE MEDICAL CENTRE

The South African Society of Otolaryngology Course in Otology will be held October 16-20, 1988. The Head and Neck Oncology Society of South Africa will hold the 3rd National Congress on October 2[illegible], 1988. Both meetings will be held at the Mount Nelson Hotel, Cape Town, South Africa. For further information, contact Deborah McTeer, Postgraduate Medical Centre, University of Cape Town Medical School, Observatory, 7925, Cape, South Africa; Telephone 471[illegible]50 ext 348.

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THE TRICYCLIC TRIMIPRAMINE IN THE TREATMENT OF SUBJECTIVE TINNITUS

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We examined 26 consecutive patients with subjective tinnitus. All subjects were treated with the tricyclic antidepressant trimipramine in a double-blind study, each subject acting as his own control. All subjects were evaluated with pure tone audiometry, site of lesion testing, and auditory brain stem evoked response. The tinnitus assessment consisted of frequency and intensity matching, the determination of masking levels, and a subjective evaluation of severity. Plasma levels of trimipramine were monitored at regular intervals, and the Zung and Millon inventories were administered at the beginning and end of each study period. Nineteen subjects completed the study. Within the trimipramine group, one reported complete disappearance of his tinnitus, eight reported improvement, three no change, and seven that tinnitus was worse. Within the placebo group, eight reported improvement, seven no change, and four that tinnitus was worse. The natural history of tinnitus is such that what has been observed may reflect the evolution of the disease itself, rather than the effect of treatment. We feel that while tricyclics may not have been shown to be effective, the placebo effect played a significant role in the results obtained.

KEY WORDS — tinnitus, tricyclic antidepressants, trimipramine.

INTRODUCTION

Subjective tinnitus is defined as the sensation of sound in the absence of any relevant external stimulus; as such, it is a symptom, not a disease. Approximately 32% of the adult population experience tinnitus; of these, 20% complain of severe, continuous tinnitus.[1] Most commonly, tinnitus is seen in association with hearing loss, although numerous other factors also are thought to play a role.[2]

The pathophysiology of subjective tinnitus is very complex. Recently, Møller[3] reviewed the currently accepted theories, one of which states that in tinnitus due to noise exposure, the cochlear insult results from deafferentation hyperexcitability. Another commonly held belief is that tinnitus is the result of an increase in the spontaneous firing rate of primary auditory nerve fibers caused by a hyperactivity of hair cells in the cochlea; another hypothesis states that this hyperactivity is localized within the auditory nerve. Other theories abound, but a full discussion is beyond the scope of this paper.

Unless a specific, treatable condition is discovered to produce tinnitus, Goodhill's statement of 1954 is still true today: "The treatment of tinnitus as a disease is an illogical dream, but the management of the patient with tinnitus is an everyday otological necessity."[4] As it previously has been reported in an anecdotal fashion that some patients with tinnitus who were given tricyclic antidepressants reported an improvement in their tinnitus, we conceived this prospective study to evaluate this observation. Pharmacologic properties of tricyclics that have the theoretic potential to suppress tinnitus are their ability to interact with the endorphin pathways and their effect on various neurotransmitter receptors. In this latter function, the tricyclics act both at the presynaptic level to increase the release of norepinephrine, and at the postsynaptic level. Among adrenergic neurons, tricyclics inhibit the postsynaptic uptake of norepinephrine and serotonin by inhibiting the membrane "amine-pump" receptor site. Tricyclics also exert a very potent postsynaptic anticholinergic effect, both centrally and peripherally.[5]

Trimipramine in particular has the most potent anticholinergic and antihistaminic effects of all the tricyclics.[6] The anticholinergic action leads to a decreased production of endolymph, and a release of inhibition of the afferent fibers of the organ of Corti and the olivocochlear bundle.[7] The antihistaminic effect, on the other hand, produces vasoconstriction of the cochlear artery. These effects are potentiated by the adrenergic properties of trimipramine, which lead to a decrease of the cochlear potential by stimulating the adrenergic perilabyrinthine network.[8]

Finally, by inhibiting the postsynaptic uptake of serotonin at the level of spinal cord neurons, trimipramine may inhibit the transmission of the tinnitus

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impulse via the auditory pathway in a manner similar to that postulated by Shea et al.[9]

In spite of having the potential side effect of tinnitus,[5] trimipramine was chosen as the tricyclic to be studied with respect to any effect that it might have on subjective tinnitus for the reasons just discussed, and because it is an effective hypnotic that can be given in a single bedtime dose.

MATERIALS AND METHODS

During the study period of November 1983 through January 1985, a total of 26 subjects were selected for participation. All were consecutive patients who presented with a chief complaint of subjective tinnitus that had failed other measures. None had disqualifying conditions, such as the wearing of hearing aids, pregnancy, or blood pressure or cardiac problems. Their ages ranged from 29 to 67 (mean, 52.3). There were 20 men and six women. Taken as a whole, the mean audiogram revealed a high frequency sensorineural hearing loss, with a mean speech reception threshold of 10 dB and a speech discrimination score of 95%. Sixteen subjects reported the hearing loss as gradual; the rest experienced it as sudden in onset. Twenty did not identify a specific cause for the hearing loss; for five the etiologic agent was noise; and in one it was secondary to a closed head injury. In all cases, the family history was negative for ear disease.

As for the tinnitus, five subjects had symptoms for 6 months to 1 year, seven for 1 to 5 years, six for 6 to 10 years, four for 11 to 20 years, and four for more than 20 years. In eight the right ear was involved, in six the left, and in 12 the sound was bilateral. Ten subjects described their tinnitus as consisting of one sound only: seven as a high pitch, one as hissing, one as crickets, and one as buzzing. The other 16 had polytonal tinnitus: seven heard two noises, four heard three, three heard four, one heard five, and one heard as many as seven different sounds. In 23 the noise was present constantly, and in three it was present more than half the time. Fourteen of the subjects reported no fluctuation, while in the other 12 cases there was fluctuation in loudness, and in two there were qualitative variations as well.

All subjects were entered into a double-blind study, with each acting as his own control. Either a therapeutic dose of trimipramine (150 mg qid) or a placebo was administered for 6 weeks, after which followed a rest period of 4 weeks, then another 6-week test period. The order in which the trimipramine or placebo was administered was counterbalanced across all subjects.

Each subject underwent a baseline medical and audiologic evaluation. The latter consisted of pure tone audiometry, site of lesion testing, and auditory brain stem evoked response. Each subject also was asked to complete a tinnitus questionnaire based on one developed by Meikle et al.[10] Subjects also underwent tinnitus and psychologic assessments. The tinnitus assessment consisted of four measurements: 1) subjective assessment of tinnitus severity (using a seven-point scale with 1 being very mild and 7 being very severe)[11]; 2) tinnitus frequency matching; 3) tinnitus intensity matching; and 4) tinnitus masking levels.[12] In order to determine if the effect observed was due to a direct action on the subject's tinnitus, and not indirectly on an underlying depression, the Zung depression inventory[13] was administered at the beginning and the end of each 6-week study period. In order to single out those patients who might be influenced by the act of being attended to, the Millon Behavioral Health Inventory[14] was administered at the same time. During the course of the study, patients were monitored with plasma levels drawn at 0-, 3-, and 6-week intervals. These were measured using high performance liquid chromatography.[15]

RESULTS

During the course of the study, seven subjects were dropped for lack of compliance. Of the remaining 19, all complained initially of some oral dryness lasting a few days, but none experienced troublesome side effects. The subjective tinnitus ratings before trimipramine administration ranged from 2 to 7, with a mean of 4.3. At the end of the drug administration period, one subject reported complete disappearance of his tinnitus, eight reported an improvement, seven felt subjectively worse, and three reported no change. The placebo administration ratings ranged from 2 to 6, with a mean of 4.0. No subjects reported the disappearance of their tinnitus following the administration of the placebo; however, eight felt their symptoms had improved, four felt they had worsened, and seven reported no change. The order in which the active or placebo form of the drug was administered had no bearing on the severity rating.

Within the trimipramine group,. the mean frequency of the tinnitus was 4,300 Hz, and it changed to 4,800 Hz at the end of the 6 weeks. The mean frequency of the placebo group was 5,800 Hz initially and 6,000 Hz at completion. These changes were found to be statistically significant. The mean intensity of the patients' tinnitus, measured as the average of three responses to the corresponding tonal frequency, actually increased during the course of the administration of trimipramine, from 46 dB to 58 dB, whereas within the placebo group it remained a constant 52 dB. These too were statistically significant changes. The mean intensity threshold at which the tinnitus was matched — that is, when the subjects admitted first hearing it — remained virtually constant for both groups: 26 dB in the trimipramine group and 28 dB in the placebo group. During the same study period, the hearing thresholds remained constant as well. The noise level required to just mask the tinnitus decreased in both groups during the course of the study period; it dropped from 70 dB to 65 dB in the trimipramine group and from 72 dB to 68 dB in the placebo group.

During the course of the study, auditory brain stem evoked responses were obtained on all subjects at both the beginning and end of each 6-week period. Trimipramine was found to improve wave morphology in some patients; however, it had no consistent effect on interwave latencies.

Plasma levels also were monitored at regular intervals; within the group receiving the placebo, no drug was detected. Within the group receiving trimipramine, the drug was detected in all subjects, confirming that they were indeed taking the medication. And in seven of the 19, a progressive increase in the plasma level could be determined. Unfortunately, there was no correlation between the plasma level of trimipramine and either the subjective or objective tinnitus response.

The psychiatric assessment consisted of the Zung and Millon inventories. The Millon inventory looked at chronic tension, recent stress, premorbid pessimism, future despair, social alienation, somatic anxiety, and pain treatment response. A significant shift in the score requires at least a ten-point change between test dates. This was seen in 12 of 19 subjects, but not in the one individual who reported disappearance of his tinnitus. The Zung inventory consisted of 25 questions, with normal scores being in the 0.25 to 0.43 range. Depressed patients usually score in a range of 0.63 to 0.90. A shift of 0.1 indicates a meaningful change. In our study, such a change was noted in four of 19 subjects, three of the four also having been identified by the Millon test as being susceptible to any therapeutic intervention. Further, only one of our subjects was noted to be depressed, and he did not respond to the medication.

DISCUSSION

The authors conducted a prospective study to determine the efficacy of using tricyclics in the treatment of subjective tinnitus. A total of 26 patients were enrolled in the study, all with the chief complaint of tinnitus and a high frequency sensorineural hearing loss. Of the 26, 19 completed the study. The mean subjective rating for the tinnitus in the trimipramine group was 4.3 (on a scale of 7), with one subject reporting complete disappearance of his tinnitus, eight reporting improvement, three no change, and seven stating that they had gotten worse. Within the placebo group, the mean subjective rating for the tinnitus was 4.0; no subjects reported disappearance of the tinnitus, eight felt improvement, seven reported no change, and four felt they had gotten worse. There also was no significant difference among the objective measurements of the two groups on mean tinnitus frequency, mean intensity of the tinnitus, mean intensity of the threshold at which the tinnitus was matched, and mean masking level.

Plasma levels of trimipramine monitored during the course of the study were difficult to quantify, but in no case was there a correlation between the level of the drug and the patient's response. In other words, neither the objective nor subjective tinnitus responses paralleled the measured plasma level of the drug. Those subjects with therapeutic levels did not show improvement, and some with subtherapeutic levels did show improvement.

By using the Millon health inventory, we were able to show that 12 of the 19 subjects would show a positive response to treatment (an observation that supports the placebo effect of therapy[16]). On the other hand, the Zung depression inventory identified only one depressed subject within the group, although all were bothered by their tinnitus. Four subjects were noted to have improved scores with therapy, however, and these same individuals also were similarly identified using the Millon inventory.

The data were analyzed using Pearson correlation coefficients and *t* tests for paired data. This analysis confirmed the validity of the subjective rating scales and of the tinnitus-matching thresholds, insofar as the pretherapy and posttherapy results correlated well with one another. It also was noted that there was an inverse correlation between the subjective rating and the subject's age, indicating that as one lived longer with tinnitus, one was able to tolerate it better. As it might be expected from our results, using multiple regression techniques we were unable to predict any significant changes in any of the variables tested over the course of the study. Since trimipramine or placebo was administered in a double-blind study counterbalanced across all subjects, the order in which these substances were administered did not influence the reported results.

CONCLUSION

Although our study does not support the hypothesis that tricyclics are beneficial in the treatment of subjective tinnitus, it does point out certain flaws in the experimental method of previous clinical trials. When conducting a study of a subjective complaint such as tinnitus, a sampling error is introduced, because the responses are checked at variable times; and though the ratings may be reliable, they may be reflecting natural variations in that complaint. Moreover, the changes in the mood of the subject, as well as his attitude toward his symptom, affect the reported results. This study indicates that though trimipramine may not be beneficial in the treatment of subjective tinnitus, the results obtained were influenced strongly by the placebo effect. This observation leads one to suspect the previously reported beneficial results of other therapies, and reinforces the need to be ever vigilant in future double-blind studies.

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AMERICAN DIOPTER AND DECIBEL SOCIETY

The American Diopter and Decibel Society will hold a combined seminar for ophthalmology and otolaryngology January 21-28, 1989, at the Acapulco Princess Hotel in Acapulco, Mexico. For further information, contact Jeannie L. Nee, Meeting Coordinator, 3518 Fifth Avenue, Pittsburgh, PA 15213; (412) 682-6300.

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ANTENATAL DIAGNOSIS OF CONGENITAL DEAFNESS

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Advances in the field of antenatal diagnosis have made possible the detection of profound sensorineural hearing loss prior to birth. Fetal motion in response to sound and auditory evoked potential testing can determine the presence of fetal hearing in the third trimester of pregnancy. Imaging modalities including ultrasound, computed tomography, and magnetic resonance imaging hold promise for the diagnosis of some forms of congenital deafness in the second trimester fetus. The methods by which congenital deafness soon may be diagnosed and the implications for the otologist are discussed.

KEY WORDS — antenatal diagnosis, congenital deafness, fetus, hearing loss, magnetic resonance imaging, ultrasonography.

INTRODUCTION

The new field of antenatal diagnosis has had a major influence upon the management of birth defects. Malformations of the CNS, heart, and urinary tract are diagnosed commonly, allowing treatment of the unborn fetus in selected cases and providing guidance to parents considering therapeutic abortion of a severely malformed fetus.[1]

It is possible to diagnose deafness before birth. Further, the technology needed to detect profound hearing loss prior to fetal viability (generally defined as 23 to 24 weeks' gestation) is upon us. Otologists soon may be called upon to provide information to parents with heritable forms of deafness and to help them with their difficult decisions.

This paper will discuss the new technologies that may establish the diagnosis of deafness and the disorders that have the potential for detection.

THIRD TRIMESTER DETECTION

Fetal hearing may be tested in the third trimester of pregnancy. As early as 1925, Peiper[2] reported an increase in palpable fetal motion in response to the sound of an automobile horn placed a few meters from the maternal abdomen. This crude experiment was refined by others to demonstrate responses of heart rate to pure tone stimuli and to define a normal range of gestational ages for this reaction.[3-6] In recent years, the fetus' blink-startle reaction to loud noise has been monitored using antenatal ultrasound imaging,[7,8] and auditory evoked potentials have been recorded in utero.[9]

Unfortunately, these stimulus-response tests all require a highly developed nervous system. In no case could a consistent reaction be elicited prior to 26 weeks of gestation. It is difficult to imagine a setting in which early delivery of a third trimester fetus or in utero therapy might be considered for hearing loss, and abortion at this advanced stage rarely is performed for even the most severely malformed fetus.[10] Thus, auditory evoked potentials and psychoacoustic testing likely will remain most valuable in postnatal application.

SECOND TRIMESTER DETECTION

If we are to predict accurately that a fetus in the early second trimester is destined not to hear, then the necessary information must come from the evaluation of cochlear anatomy, as the labyrinth is formed well before its neural connections are completed.[11] Further, if deafness is to be diagnosed in utero based upon morphologic criteria, three conditions must be met. First, the malformation sought must be gross enough that an imaging device can detect it. Second, the presence of such a malformation must predict accurately that hearing loss will result. Third, the malformation must occur with high frequency, follow a known genetic pattern, or be associated with other, more conspicuous anomalies so that investigators will know when to look for it (Table[12-21]). These are rigorous constraints, which will be satisfied by only 10% of cases of congenital deafness.

A model for a diagnosable cause of congenital deafness is offered by the Pendred's syndrome of heritable sensorineural hearing loss and goiter. It is common, comprising 2% to 10% of all congenital deafness, has a one-in-four risk of recurrence in future pregnancies, and displays a gross cochlear defect in up to 50% of cases.[13,14]

The gross cochlear malformations most consistently associated with deafness are the Michel and Mondini types.[16] In the Michel deformity, the labyrinth is reduced to a cystic cavity or is totally absent, resulting in deafness in all known cases.[15,19,22] In the Mondini dysplasia, the cochlea is shortened and flattened and there are varying degrees of vestibular abnormality.[23-25] When the Mondini dysplasia is severe (ie, cochlea less than $1\frac{1}{2}$ turns),

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GENETIC SYNDROMES WITH HIGH RECURRENCE RISK AND MACROSCOPIC MALFORMATION OF INNER EAR

Syndrome	*Genetics*	*Labyrinthine Malformation*	*Key to Antenatal Syndrome Diagnosis*
Isolated Mondini dysplasia[12]	AD, AR	Mondini type	None
Pendred's syndrome[13,14]	AR	Mondini type (50%)	None
Atresia auris congenita[12,15]	AD	Variable, Michel type reported	Pinna malformations by ultrasound
Achondroplasia[12]	AD	Deformed cochlea with thickened partitions	Skeletal malformations by ultrasound
Wildervanck's syndrome[13,16]	?AD, ?X-linked lethal	Cochlea reduced to cavity, deficient modiolus	Cervical vertebral malformations by ultrasound
Waardenburg's syndrome[17]	AD	Hypoplasia of cochlea and semicircular canals (rarely)	None
Treacher Collins syndrome[18]	AD	Absent or severely malformed cochlea and vestibular apparatus	Craniofacial malformations by ultrasound
Trisomies 13, 18, and 21 if associated with balanced parental translocation[19-21]			Karyotype by amniocentesis

AD — autosomal dominant, AR — autosomal recessive.

hearing loss is consistently profound.[26]

Several radiologic techniques have the potential to diagnose such gross morphologic changes of the cochlea. The most promising are antenatal ultrasound, computed tomography, and magnetic resonance imaging.

The diagnostic technique most commonly used to study the human fetus is antenatal real-time ultrasound. Ultrasound is capable of visualizing fetal structure well, as the amniotic fluid about the fetus is a good conductor of sound waves. In the adult, ultrasound is not used to study the cranium or its contents, as sound waves cannot penetrate its solid bone. In the fetus, however, ultrasonic waves can pass through the thin, membranous bone of the calvaria and are reflected from acoustic interfaces within the brain and its ventricular system. These reflected sound waves are analyzed and transformed into images of fetal anatomy. Recently, it was demonstrated that some of these sound waves penetrate the petrous apex in those areas in which the labyrinth is covered by only a few millimeters of partially mineralized bone.[27] In this way, an outline of portions of the superior and posterior semicircular canals, their crus commune, and the basal turn of the cochlea may be visualized (Fig 1). This rudimentary picture of the inner ear's structure probably is sufficient to diagnose the Michel type of inner ear malformation.

Ultrasound has another application in the search for structural abnormalities of the ear. The pinna of the ear projects into the amniotic fluid, allowing detailed study of its shape and the development of its cartilages.[28] Deformities of the pinna and aural atresia are associated with a variety of middle ear malformations[12] and with inner ear defects in up to 12% of cases.[15,29] Thus, detection of an external ear abnormality by ultrasound serves as a marker for more serious structural aberrations and should prompt further antenatal study.

Antenatal ultrasound, as a single modality, is limited in its ability to diagnose congenital deafness. The inner ear is visualized inconsistently, and the usual ultrasound examination, performed to establish gestational age and fetal well-being, likely would miss the common cochlear defects. The de-

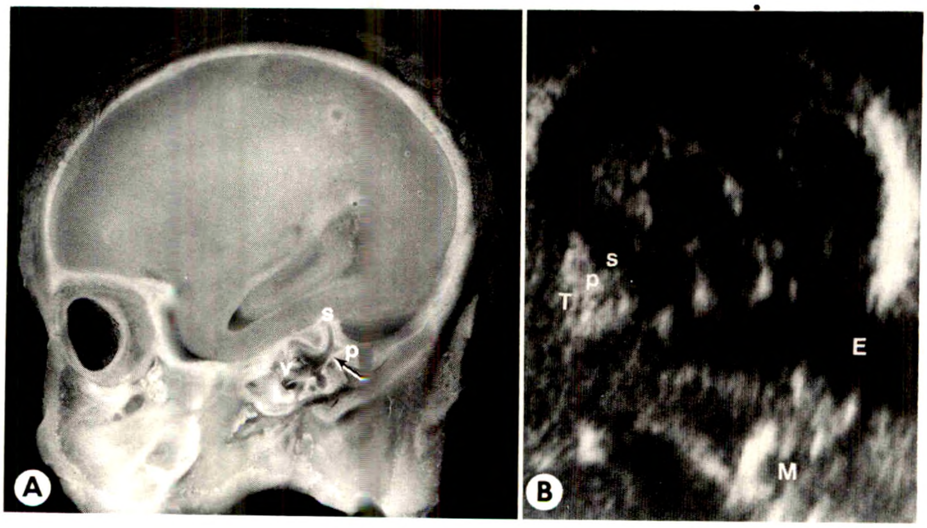

Fig 1. Sagittal section of fetal head. A) Gross section. v — vestibule, s — superior semicircular canal, p — posterior semicircular canal, arrow — crus commune. B) In utero ultrasound image at 20 weeks' gestation. T — temporal bone, M — mouth, E — eye. (Modified from Isaacson and Mintz.[27])

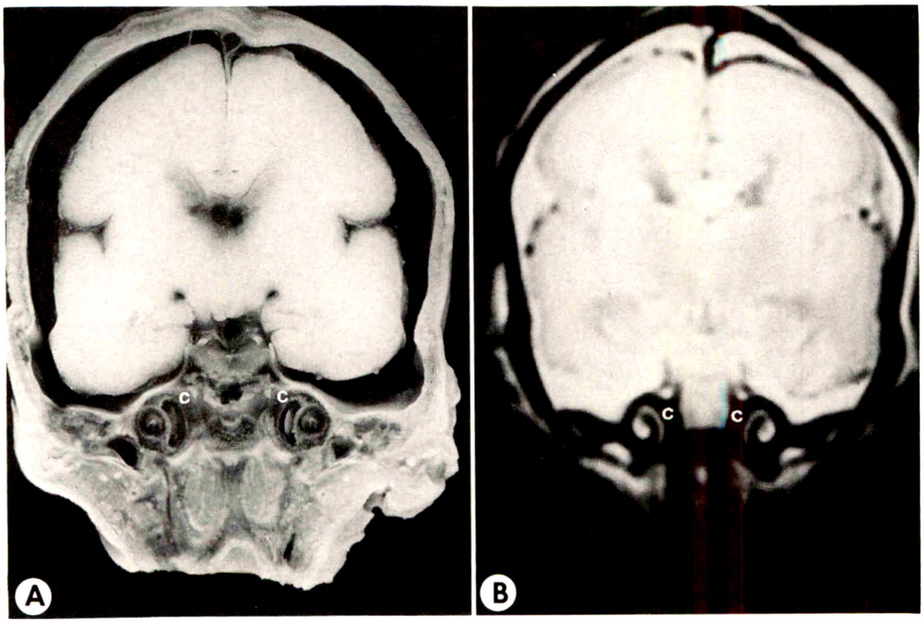

Fig 2. Coronal section of fetal head. A) Gross section demonstrating large cochlea and its thin bony roof. B) Abortus. Magnetic resonance imaging with strong signal emitted from cochlear duct. c — cochlea. (Modified from Isaacson et al.[36])

tection of the Mondini defect requires an imaging technique of greater resolution, which can detect subtle changes in the shape and length of the cochlea. Computed tomography has diagnosed the Mondini malformation successfully in adults.[30] Since the fetal cochlea has reached nearly its full adult size by 20 weeks of gestation,[31] it is likely that current CT could visualize the Mondini defect in utero as well. When a malformation syndrome that includes the Mondini defect has been detected by ultrasound or amniocentesis, and the coexistence of deafness might affect parental decisions, in utero CT should be considered. Computed tomography is not a desirable antenatal scanning technique, however, as it delivers a significant dose of ionizing radiation.[32]

Perhaps the best hope for diagnosing deafness in the second trimester of pregnancy is offered by MRI, which uses intense magnetic fields and radio frequency signals to produce sectional images in axial, coronal, or sagittal planes. Its ability to identify inner ear anatomy and pathology in adults has been demonstrated,[33] and preliminary studies of fetal anatomy are ongoing.[34,35]

Magnetic resonance studies of the ears using special research equipment have produced detailed pictures of inner ear anatomy in aborted fetuses.[36] Bone generates no signal by MRI, but fluid within the labyrinth does, and this fluid delineates the shape of the cochlea, vestibule, and semicircular canals (Fig 2).

Additional information about cochlear structure can be derived from an MRI modification by which hyaline cartilage emits a signal. The modiolus and outline of the cochlea are still cartilaginous at 20 weeks' gestation and may be evaluated by this method (Fig 3).[37,38]

Temporal bone images of high quality have not

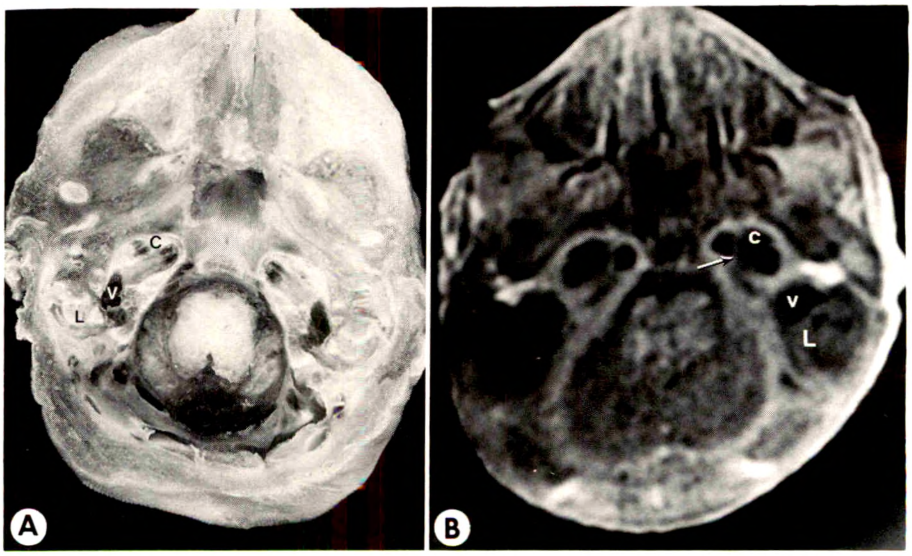

Fig 3. Axial section of fetal head. A) Gross section. B) Abortus. Magnetic resonance imaging (T1 weighted). C — cochlea, V — vestibule, L — lateral semicircular canal, arrow — modiolus. (Modified from Isaacson et al.[37])

yet been produced in utero, as the second trimester fetus often moves during the 2 to 3 minutes required to complete a scan. Within a year, however, new software will reduce scan time to a few seconds, and advances in surface coil techniques will improve resolution further.

As our ability to detect increasingly milder aberrations in fetal anatomy expands, the scientific and moral problems facing both physicians and parents grow more complex. The potential for diagnosis of isolated deafness in early gestation brings such issues to bear on otolaryngology.

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Ann Otol Rhinol Laryngol 97:1988

REDUCTION OF SALIVARY FLOW WITH SCOPODERM TTS

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Scopoderm transdermal therapeutic system (TTS) is a form of application permitting programmed release of scopolamine through the skin into the bloodstream. Scopoderm TTS is indicated for prevention of nausea and vomiting associated with motion sickness. The most common side effect associated with its use is dryness of the mouth. We have been using Scopoderm TTS for reducing salivary flow in patients with sialorrhea or with difficulties in swallowing normal amounts of salivary secretions. Good results were achieved with minimal discomfort from adverse effects. We recommend the use of Scopoderm TTS in selected cases of sialorrhea and drooling, preoperatively and postoperatively in patients undergoing surgery of oral, laryngeal, and pharyngeal lesions.

KEY WORDS — salivation, sialorrhea, Scopoderm TTS, scopolamine.

INTRODUCTION

Scopoderm transdermal therapeutic system (TTS; ALZA Corp, United States, for CIBA-GEIGY, Ltd, Switzerland) is applied to prevent nausea and vomiting associated with motion sickness, permitting programmed release of scopolamine in a free base form through the intact skin into the bloodstream. The system is a circular filmlike patch, 1.8 cm in diameter and 0.2 mm thick. It consists of an impermeable backing layer, a drug reservoir containing 1.5 mg scopolamine, a rate-controlling microporous membrane, and an adhesive providing contact with the skin[1-3] (Figure, A).

Approximately 140 μg of scopolamine is delivered as a loading dose in the first few hours, followed by a release rate of approximately 5 μg per hour.[1-3] Equilibrium between absorption and elimination is reached after about 6 hours and is maintained for 72 hours, unless the system is removed earlier.[1-3] Optimum absorption occurs when the system is applied to the hairless skin behind the ear[1] (Figure, B).

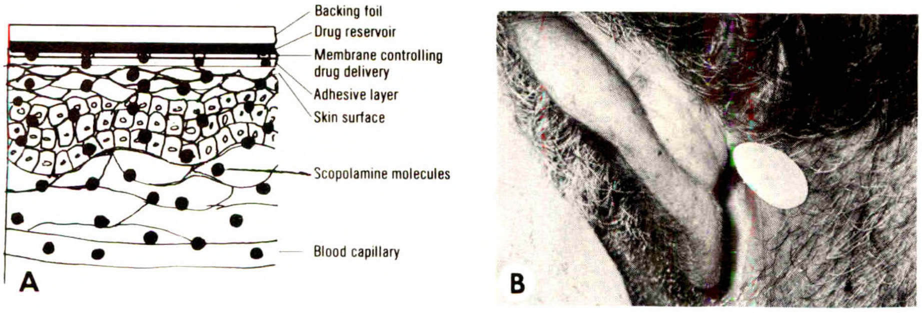
Scopolamine (hyoscine) is one of the family of natural alkaloids, *Atropa belladonna*, and is a cholinergic muscarinic receptor antagonist.[4] Scopolamine normally has undesirable side effects such as mydriasis, cycloplegia, urinary retention, and dry mouth.[4,5] Research shows that the effect of reducing salivary secretion is more prominent than with the use of atropine.[4] Dry mouth is recognized as the most common adverse effect of the use of Scopoderm TTS and appears in up to two thirds of patients treated.[1-7] The onset of its effect in reducing secretions may begin as soon as 15 minutes from the time of application.[8]

Otolaryngologists frequently encounter sialorrhea, usually causing drooling. Drooling also may occur when a patient does not regularly swallow saliva that is secreted in normal amounts, such as in patients with painful lesions of the mouth or throat, paralysis of the tongue or pharyngeal constrictor muscles, and stenosis or obstruction of the esophagus.

After surgery of the oral cavity, floor of the mouth, tongue, larynx, or pharynx, patients may have great difficulty in swallowing saliva. Repeated suctioning may hamper healing, cause local trauma and discomfort for the patient, and be an additional burden for the attending personnel. We applied Scopoderm TTS to selected patients in our department to try to reduce salivary flow.

MATERIALS AND METHODS

Twelve patients hospitalized in the past 10 months were included in the treatment group (Table). Pa-



Scopoderm TTS. A) Schematic representation of patch. B) Subject with patch applied to postauricular area.

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PATIENTS TREATED WITH SCOPODERM TTS

Pt	*Age*	*Sex*	*Diagnosis*	*Surgery*	*Time of Application (d)*	*Salivary Flow Reduction*	*Side Effects*	*Comment*
1	70	M	Ca of larynx	TL and R RND	1	+	– – –	Urinary retention
2	50	M	Ca of floor of mouth	L RND; Excision of floor of mouth and mandibilectomy with R RND	3	+ +	0	
3	47	M	Ca of tongue	Total glossectomy with R RND	6	+ + +	–	
4	71	M	Supraglottic ca of larynx, stridor, difficulty swallowing	Tracheostomy	6	+	–	
5	36	F	Cyst of parotid gland; severe stasis of deep lobe after surgery	Superficial parotidectomy and ligation of Stenson's duct	4	+ +	–	
6	37	M	Supraglottic ca	Supraglottic laryngectomy	3	+ +	0	
7	55	F	Advanced ca of cervical esophagus; infiltration of trachea; blocked esophagus and stridor	Tracheostomy	2	+	–	Patch applied preoperatively and postoperatively
				TL, pharyngectomy, esophagectomy; reconstruction of esophagus by gastric tube	4	+	0	
8	12	F	Chronic drooling; cerebral palsy patient		3	+ + +	0	Patient scheduled for surgery; patch on for confirmation celebration
9	50	M	Severe retardation, huge goiter		2	0	0	
10	76	F	Ca of tongue	Partial glossectomy	3	+ +	– –	
11	65	M	Ca of tongue	Partial glossectomy	3	+ +	–	
12	38	M	Condition after laryngectomy for supraglottic ca	Postradiation treatment and chemotherapy with local edema	2	0	0	

Ca — carcinoma, TL — total laryngectomy, RND — radical neck dissection. Salivary flow reduction: none (0), mild (+), good (+ +), very good (+ + +); side effects: none (0), mild (–), tolerable (– –), discontinuation of treatment (– – –).

tients with cardiac problems, glaucoma, or hypertrophy of the prostate were excluded. One patient refused treatment. Informed consent was given by each patient or by his or her custodian.

The Scopoderm TTS patch was applied to the skin behind the ear after cleansing with 70% alcohol. Application was made after the patients awoke from narcosis and had urinated. Patches were removed after 4 days at the most; new ones were applied, usually after 3 days, when treatment was continued. No truly objective measurement was taken; results were assessed by the authors according to the number of suctioning procedures needed and by the patients' subjective reports every 4 hours, when possible. Eye examination for mydriasis and blood pressure measurements were taken twice daily. Blurring of vision and impairment of concentration were assessed according to patients' complaints.

Patient No. 7 was treated with Scopoderm TTS for sialorrhea ensuing from dysphagia due to her advanced stage tumor, and was treated again after surgery because of inability to swallow adequately.

RESULTS

One patient developed urinary retention, and though results were considered good, treatment was discontinued after less than 24 hours. Of the other patients treated, all but two showed some favorable results. There was no basic contradiction between the patients' reports and our observations. Side effects, mainly blurring of vision, caused only minimal discomfort to four patients. No local skin reaction was seen in any of the patients.

DISCUSSION

Sialorrhea accompanied by drooling is a common, stigmatizing problem in neurologically damaged patients, such as those suffering from cerebral palsy, paralysis agitans, familial autonomic dysfunction, and myasthenia gravis. It has been described in diabetes and in diseases of the pancreas. It is common among patients with retardation or mental illness such as schizophrenia. Various modalities of treatment have been suggested: physiotherapy, external radiation, anticholinergic medications, hynotherapy, biofeedback techniques, intensive speech therapy, and conditioning procedures.[9,10] Various surgical methods were suggested: submandibular duct relocation,[10] parasympathetic nerve section,[11] direction of salivary flow to the pharynx with or without excision of the submandibular salivary gland,[13] tympanic neurectomy, and chorda tympanectomy.[12,13]

All these methods have been tried with varying degrees of success. Scopolamine (hyoscine) has been known since 1872 to reduce salivary flow.[4] Its use has been limited severely because of its inadequate and irregular absorption, and because of the severity of side effects induced when taken orally or parenterally.[1,2,5]

The transdermal delivery system allows plasma concentration of scopolamine to reach a fixed therapeutic level. Reported use of Scopoderm TTS,[5] and our use of it for vertigo in patients who experienced dry mouth as a side effect, led us to try using it for reducing salivary flow. We were especially interested in assessing Scopoderm TTS's effect on patients with temporary difficulties in swallowing, such as our postsurgical patients, as well as special cases of chronically drooling patients.

As some middle-aged patients suffer from hypertension, glaucoma, or benign hypertrophy of the prostate, Scopoderm TTS is relatively contraindicated for them. As for other patients, special care was taken, after ruling out these disorders, to apply the patch only after urine was passed. The relatively intensive monitoring allowed us to receive early warning of any unwanted side effects. As stated, in only one patient was treatment discontinued.

Two authors[8,15] suggest the use of Scopoderm TTS for this purpose. Dettman[8] suggested its use for suppression of salivation in wind instrument players. Rogawski[15] reported a case of a 57-year-old patient suffering from amyotrophic lateral sclerosis with drooling, whom he treated with Scopoderm TTS with temporary relief of the patient's problem.

No information on long-term treatment with Scopoderm TTS was available. The longest treatment period was 6 days,[16] with exchange of the unit after 3 days, or 7 days with one unit. Scopoderm TTS also may be used in chronically drooling patients for special, short-term occasions; one patient had the patch applied for a religious confirmation ceremony.

Naturally, without sufficient data we did not attempt long-term treatment. We recommend the short-term use of Scopoderm TTS in patients for reducing salivary flow.

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Ann Otol Rhinol Laryngol 97:1988

AURAL PAIN RESULTING FROM ACOUSTIC REFLEX

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We present an unusual case of physical discomfort, as opposed to objective or subjective tinnitus, caused by a unilateral acoustic reflex. The cause of the discomfort was identified audiologically by the use of acoustic impedance audiometry. The dull pain that was elicited upon contraction and relaxation of the stapedius muscle was eliminated with sectioning of the stapedial tendon. No explanation of the mechanism for the pain is suggested at present.

KEY WORDS — acoustic impedance testing, acoustic reflex, osteoma, stapedius muscle.

Several accounts of unusual tinnitus caused by the acoustic reflex have been presented in the literature. One account by Rock[1] described the tinnitus as a "whishing" sound, and another by Sheehy and Hughes[2] described it as a "clicking." In still another account, Rock[3] described an objective tinnitus that both he and the patient could hear upon contraction by the patient's middle ear muscles. Williams[4] described a case in which a patient's steady tinnitus would fluctuate in subjective loudness when the patient blinked his eyes. In none of these cases, however, did the patient complain of physical pain in the aural area accompanying the annoying tinnitus. A different set of neural circumstances would be suspected when a patient presents with physical pain instead of tinnitus as a result of the acoustic reflex.

A 35-year-old man presented to the senior author in Tahlequah, Okla, with a 5-year history of physical discomfort in the right ear elicited by certain types of environmental sounds. The sensation was described by the patient as a "dull" pain with two distinct phases corresponding to the onset and cessation of the offending sounds. The patient reported no tinnitus involved with the sensation. Any intense, sudden-onset sound such as a fork falling to a plate, coins hitting a coin tray, or the ringing of an electric doorbell would initiate the sensation. The patient had no significant history of head trauma, chronic middle ear disease, prolonged noise exposure, or acoustic trauma.

Pure tone audiometry results indicated normal hearing thresholds bilaterally (right PTA = 10 dB HL) except for a 20-dB sensorineural dip at 4,000 Hz in the right ear. Speech reception thresholds were 10 dB HL bilaterally, and speech discrimination scores were 100% in both ears when the Central Institute for the Deaf, St Louis, W-22 words were presented at a level of 40 dB HL. Acoustic impedance testing resulted in normal type A tympanograms for both ears with acoustic reflexes being present contralaterally for frequencies 500, 1,000, 2,000, and 4,000 Hz at intensity levels between 90 and 105 dB HL.

It was during the routine acoustic reflex testing that the patient reported the recurrence of the sensation in the right ear. Further study demonstrated that the sensation was present in two phases whenever the patient's acoustic reflex was elicited. This was true not only for pure tones, but also for noise and speech. The first phase of the sensation was a feeling of momentary pain and a tightness in the ear that corresponded to the onset of the stimulus. The second phase, which immediately followed cessation of the stimulus, was recurrence of the pain and relief of the tightness that was present for the duration of the stimulus. It was also possible to elicit the acoustic reflex, and more importantly the sensation, by tactile stimulation of the right ear. With the impedance probe inserted in the right ear, it was possible to view compliance changes resulting from light stroking of the right tragus, which occurred concomitantly with the patient's reported sensations. Because Djupesland[5] observed that the change in impedance elicited via tactile stimulation was caused most often by contraction of the stapedius muscle alone, these results were thought to show conclusively that the patient was feeling the uncomfortable sensation upon contraction and relaxation of the stapedius muscle in his right ear. The patient was told of the results and advised that lysis of the stapedial tendon most likely would relieve the uncomfortable sensation.

Under general anesthesia, a tympanomeatal flap with a long sleeve of 8 mm was created. Exposed with the flap was a large anterior canal wall osteoma. The osteoma did not contact the tympanic membrane. The osteoma was removed with a bur, and the entire tympanic membrane was visualized. The bur was further used to remove a large posterior bony shelf obscuring the stapes. Visualization of the stapes, stapedial tendon, and the pyramidal

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eminence was obtained. The stapedial tendon then was crushed and transected. The tympanomeatal flap was replaced. Postoperatively, the ear healed uneventfully. Audiologic testing performed 10 months postoperatively showed no acoustic reflex in the right ear. The uncomfortable sensation also was eliminated.

Two possible explanations for resolution of the patient's uncomfortable sensation exist, the first and less likely being that it was caused by the osteoma and was eliminated by removal of the osteoma. This seems unlikely, because there was no contact with the tympanic membrane. The second and more likely explanation is that the motion of the stapedial tendon itself caused the discomfort. The mechanism of this discomfort cannot as yet be explained and to our knowledge has not been described previously.

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THE DEAFNESS RESEARCH FOUNDATION
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The Deafness Research Foundation's Otological Research Fellowship will be sponsored by a department of otolaryngology conducting otological research. Where a unique opportunity exists in a related discipline, the fellowship may be conducted in that discipline while maintaining liaison with the department of otolaryngology. The fellowship would be scheduled as a one-year block of time at the end of the third year of medical school, thus requiring a one-year leave of absence from the medical school curriculum. Applications for 1989 must be received by November 15, 1988. For more information, please contact Walter A. Petryshyn, MD, Medical Director, The Deafness Research Foundation, 9 East 38th Street, New York, NY 10016; (212) 684-6556.

Ann Otol Rhinol Laryngol 97:1988

HIGH FREQUENCY AUDIOMETRY IN PROSPECTIVE CLINICAL RESEARCH OF OTOTOXICITY DUE TO PLATINUM DERIVATIVES

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The results of clinical use of routine high frequency audiometry in monitoring the ototoxic side effects of platinum and its derivatives are described in this prospective study. After demonstrating the reproducibility of the technique, we discuss the first results of an analysis of ototoxic side effects in 75 patients (150 ears). Significant differences in the pattern of hearing loss were registered for the different platinum treatment groups (cisplatin 20 mg/m², cisplatin 50 mg/m², and carboplatin 350 mg/m²). In the groups receiving cisplatin 50 mg/m² and carboplatin 350 mg/m², 42% and 25%, respectively, of the investigated ears proved to be undamaged, versus 9% undamaged in the group receiving cisplatin 20 mg/m² ($p < .01$). Ototoxic hearing loss started mainly (46% to 70%) in the higher frequencies (10,000 to 18,000 Hz) and developed into a broader-range hearing loss (1,000 to 18,000 Hz) during treatment in 13% to 43% ($p < .01$). The onset of hearing damage was influenced by the patient's age ($p < .001$) and the existence of a troubled otologic history ($p < .05$). The study demonstrates the important role of high frequency audiometry in early detection and monitoring of ototoxic damage.

KEY WORDS — audiometry, carboplatin, cisplatin, high frequencies, ototoxicity.

INTRODUCTION

Cis-diamminedichloroplatinum, or cisplatin, is an effective antineoplastic agent. It has an established role in the treatment of nonseminomatous germ cell tumors, ovarian carcinoma, and squamous cell carcinoma of the head and neck. The associated side effects of cisplatin include nephrotoxicity, myelosuppression, gastrointestinal dysfunction, ototoxicity, and vestibulotoxicity. From a clinical point of view, ototoxicity is not a life-threatening complication; but it should not be underestimated. At first, cisplatin was thought to cause toxic side effects in the cochlea only incidentally and probably even reversibly. Recently, it has been suggested that the incidence of ototoxicity varies from 4% to 91%.[1-9] Unfortunately, it is not possible to compare different studies because of the various definitions used for ototoxicity. Most authors based their clinical studies on serial audiometry for frequencies up to 8,000 Hz. Patients were considered to have a significant hearing loss if serial audiometry showed a drop of 15 dB or more in pure tone threshold in one ear, or a drop of 10 dB or more in both ears at one or more frequencies. Usually some of the following factors were indicated to influence the onset of ototoxic damage: cumulative dose, individual dose, age, kidney function, preexistent hearing loss, and the simultaneous administration of more than one ototoxic drug. The various studies are lacking in uniformity, especially with regard to dose schedules. Experimental studies in which cisplatin was administered to guinea pigs and monkeys showed a remarkable dose-dependent loss of hair cells over the complete length of the basilar membrane, with a preference for the basilar turn of the cochlea.[10] Even the stria vascularis showed severe degenerative changes. Based upon these experimental findings, we were interested in studying these ototoxic side effects in a clinical setting, with special interest in the functioning of the hair cells in the basal turn, ie, performing audiometry for the high frequencies (HFs).

Only Jacobson et al,[11] Osterhammel,[12] and Fausti et al[4,13] mentioned clinically applied HF audiometry with patients treated with cisplatin or other ototoxic drugs. They described the early effects of ototoxic damage, especially in the perception of the HFs. High frequency loss was detected some time before the patient complained about tinnitus or vertigo, or before damage could be demonstrated in the conventional pure tone audiogram.

Using the technique introduced by Fausti et al,[4,13] HF audiometry was applied in our department for patients treated with platinum and its derivatives. In the present study, we report the results of periodic HF audiometry prior to each successive cycle of treatment, aiming at answering the following questions.

1. What is the role of audiometry in early detection of ototoxicity?
2. Do cisplatin and carboplatin have different patterns of ototoxicity?
3. What are the possible risk factors in the development of ototoxic damage?
4. Is there a significant dose-related pattern of ototoxicity?

MATERIALS AND METHODS

Patients. In collaboration with the oncologic

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department of our university clinic and the Antoni van Leeuwenhoekhuis, audiometric investigation was performed in 142 patients with various types of malignancies. All patients received platinum products (cisplatin, carboplatin) as a single drug or in combination with other antineoplastic agents. The diagnosis was most frequently ovarian cancer or testicular cancer; but head and neck cancer, cancer of the uterine cervix, osteosarcoma, and other malignancies were encountered as well.

Audiometry. After an otologic examination and interview, all patients underwent a standard audiometric investigation. This included pretreatment audiometry, audiometry at approximately 3-week intervals, and, for most, posttreatment measurements. In the pretreatment stage, conventional audiologic assessment was performed, ie, pure tone thresholds (including bone conduction thresholds) and baseline speech audiometry, as well as HF audiometry. Between the treatment courses, baseline speech audiograms and/or tympanometry were performed only on clinical indications, besides the usual pure tone and HF audiometry.

Pure tone thresholds from 250 Hz to 8,000 Hz were determined using an Interacoustics AC4 audiometer and TDH-39 headphones. Pure tone thresholds from 8,000 Hz to 20 kHz were determined using a Demlar HF audiometer and dynamic earphones with a ceramic diaphragm (KOSS HV/IA). These procedures are described in detail by Fausti et al.[4,13]

In an earlier study,[14] based upon 180 audiograms, the standard deviation of repeated threshold measurements proved to be within the range of 4.3 dB for each frequency (250 to 20,000 Hz). In view of the magnitude of ototoxic damage, this level of precision seemed to be sufficient.

Prospective Clinical Research. We collected the results of all 75 patients who were submitted to at least three HF audiograms. Patients not included in this study were patients who died during treatment, patients with frequent changes in treatment schedules, and patients with less than three HF audiograms. Besides the various types and dosages of the drugs administered, the patients were categorized according to the following characteristics. Twenty patients were between 0 and 30 years of age, 13 were between 30 and 45, 21 were between 45 and 60, and 21 were 60 and over. Thirty-two patients were male, and 43 were female. Forty-seven patients had uneventful otologic histories; and 28 had histories of otologic disease, such as previous antineoplastic drug treatment, abnormalities shown by the otologic examination and interview, or signs of noise exposure or conductive hearing loss measured in the pretreatment stage.

Definitions. In this study we worked with separate ears, rather than with a combination of the two ears of each subject. Hence the ototoxic side effects of platinum derivatives upon 150 ears from 75 subjects have been analyzed. As an objective criterion of ototoxicity, we used the following definition: 20 dB or more deterioration at one frequency, 15 dB at two frequencies, or 10 dB at four frequencies. For several reasons, we preferred this more conservative criterion (Dreschler et al[14]).

In monitoring ototoxicity, we distinguished threshold deteriorations in three frequency regions: 1) low frequency (LF) region (1,000 to 8,000 Hz); 2) high frequency (HF) region (10,000 to 18,000 Hz); and 3) both low and high frequency (BF) regions. Nine patterns of damage development were differentiated when combining the frequency region in which the onset of ototoxic damage was most pronounced with the frequency region in which the final deterioration was found. For example, HF ototoxicity, as onset damage, can change during the treatment into LF deterioration or BF deterioration, or it can persist as HF ototoxicity.

We used a Digital 1123 computer for analysis and for generation of graphics.

RESULTS

In this study, 75 patients fulfilled the conditions mentioned above (at least three HF audiograms). This group could be divided into three groups, according to three different types of antineoplastic drug treatment.

In group A, 51 patients were treated with cisplatin 20 mg/m², administered daily by a 4-hour infusion for 5 consecutive days. Each course of chemotherapy was separated by 28 days.

In group B, 12 patients were treated with cisplatin 50 mg/m², administered once every 4 weeks by a 4-hour infusion.

In group C, 12 patients were treated with carboplatin 350 mg/m², given by a half-hour infusion once every 5 weeks.

Cisplatin and carboplatin were administered in multidrug regimens. The other chemotherapeutic drugs included doxorubicin, cyclophosphamide, hexamethylmelamine, vinblastine, bleomycin, etoposide, and adriamycin, none of which is known to be ototoxic in doses currently used in human antitumor therapy. We analyzed treatments varying from three to ten chemotherapeutic courses. The average number of HF audiograms was five.

Figure 1A shows the results of group A. In the group that received cisplatin 20 mg/m², 9% received no damage (first vertical bar), 2% received inconsistent damage (second vertical bar), 12% received LF onset damage (third vertical bar), and 8% received BF onset damage (fourth vertical bar).

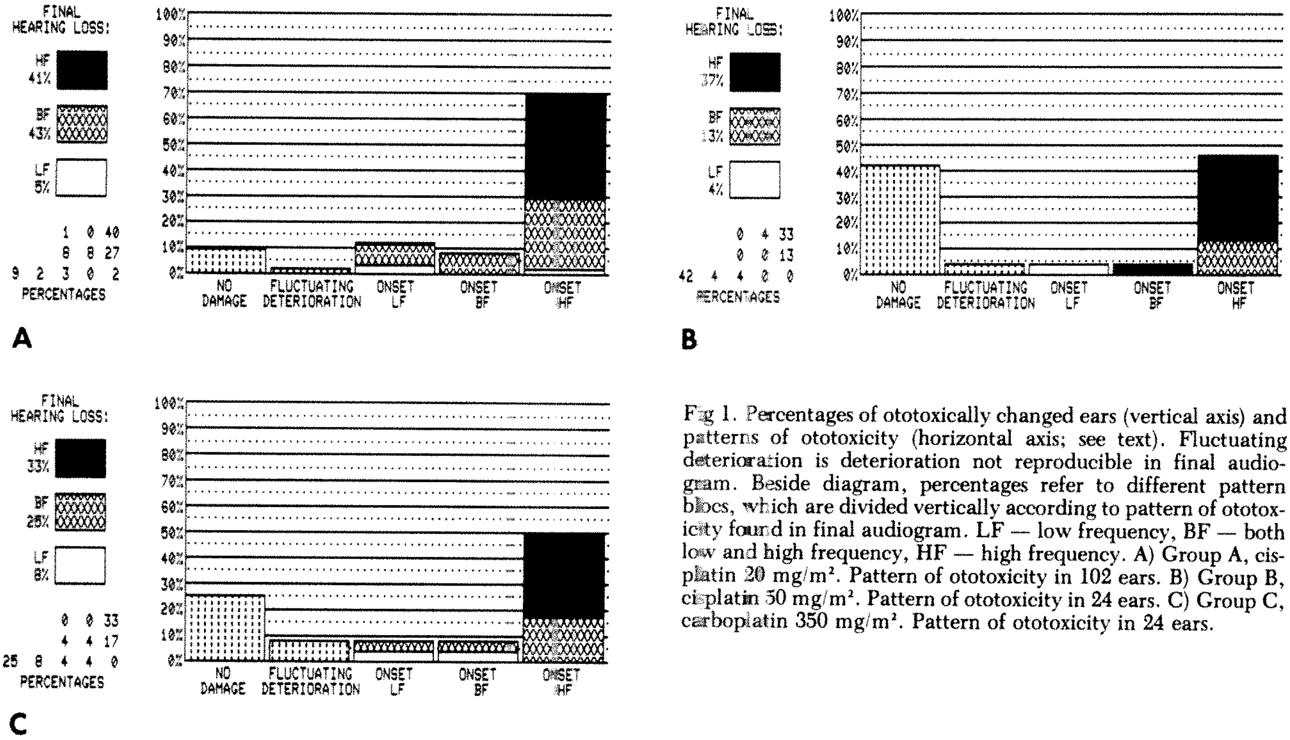

Fig 1. Percentages of ototoxically changed ears (vertical axis) and patterns of ototoxicity (horizontal axis; see text). Fluctuating deterioration is deterioration not reproducible in final audiogram. Beside diagram, percentages refer to different pattern blocs, which are divided vertically according to pattern of ototoxicity found in final audiogram. LF — low frequency, BF — both low and high frequency, HF — high frequency. A) Group A, cisplatin 20 mg/m². Pattern of ototoxicity in 102 ears. B) Group B, cisplatin 50 mg/m². Pattern of ototoxicity in 24 ears. C) Group C, carboplatin 350 mg/m². Pattern of ototoxicity in 24 ears.

In the latter groups, the final pattern was predominantly BF hearing loss. The 69% HF onset damage (fifth bar) is remarkable, with 40% remaining HF final hearing loss and 27% developing to BF final hearing loss. In this HF audiometry diagram, it can be seen that the final loss remained restricted to the HF region in 41% of the cases, whereas in 48% of cases the LF region had deteriorated, the latter consisting of 43% BF and 5% LF final hearing impairment.

Figure 1B,C shows the different patterns of onset versus final deterioration in groups B and C. Group B (cisplatin 50 mg/m²) and group C (carboplatin 350 mg/m²) seemed to develop different patterns of ototoxicity. Although more pronounced in Fig 1B, both groups B and C show far more ears with no damage (42% and 25%, respectively) and equal LF and BF ototoxicity. The HF onset damage is again the largest group, although the percentages (46% and 50%, respectively) are lower than in group A. For these cases, the turnover to a final BF hearing loss seems less pronounced. The differences found in the three patient groups proved to be significant ($p < .01$) when using the χ^2-square test for independent samples.

Figure 2 shows the pattern of ototoxicity in group A (cisplatin 20 mg/m²) with regard to the issue of age. Almost all 40 ears (age of the patients 0 to 30 years; the youngest 17 years of age) in Fig 2A show an HF onset damage, whereas the majority do not develop BF ototoxicity in the final stage. The LF, BF, and no-damage groups are negligible. In Fig 2B (age 30 to 45 years), the pattern of ototoxicity onset does not differ from that of the younger group; 55% of ears developed BF damage finally, after an HF onset.

With increasing age, the final damage seemed to be more concentrated in the LF range, whereas the onset damage shifted from the HF to the BF region. In the oldest group, finally, the pattern of onset damage was not quite consistent; this could be caused by the fact that older patients show significantly less HF perception and therefore supply only a few HF thresholds in HF audiometry. Nevertheless, the changes in onset of hearing loss related to the four age groups were highly significant ($p < .001$).

It should be emphasized that in the age-selected groups some distribution of tumors could be recognized. The nonseminomatous germ cell tumors were seen in the two younger groups, whereas ovarian cancers were rare in the group 30 to 45 years of age but frequent in patients older than 45 years. This distribution of tumors makes it difficult to correlate hearing loss with gender; hence this relationship will not be discussed here.

Finally, in comparison with the group of patients with uneventful otologic histories, the patients with troubled otologic histories showed a preponderance of BF over HF onset damage ($p < .05$). The patterns of final damage were not significantly different according to otologic history.

DISCUSSION

This study shows that ototoxic damage due to platinum derivatives is not limited to the conventional range of audiometric frequencies. This is a

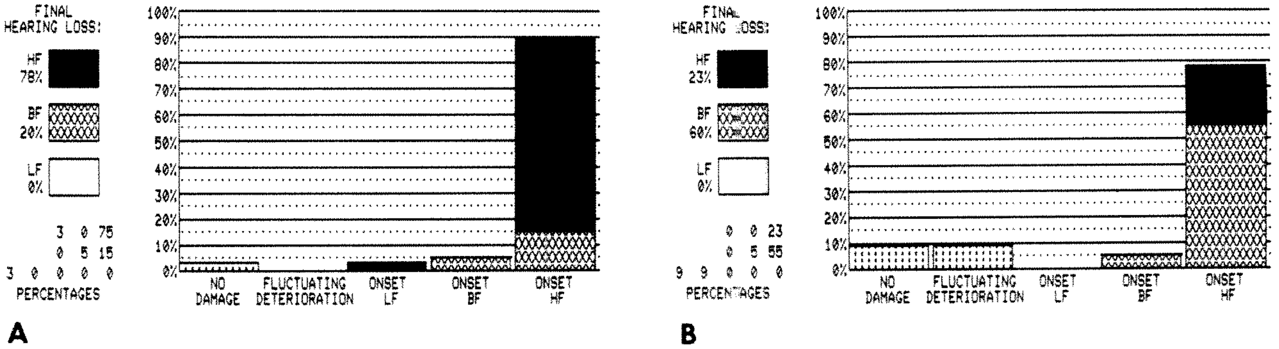

Fig 2. Group A. Patterns of ototoxicity in A) 40 ears of patients 0 to 30 years of age and B) 22 ears of patients 30 to 45 years of age.

clinical confirmation of the results of several animal studies[10,15] in which remarkable loss of hair cells over the complete length of the basilar membrane was demonstrated, with a preference for the basilar turn of the cochlea. As described in Tange et al,[16] HF audiometry is an important tool in early detection of this ototoxic damage. The reproducibility of HF audiometry, using standard audiometric procedures, is almost as good as for the conventional range of frequencies.[14] While using a highly sensitive procedure with many threshold frequencies (250 to 18,000 Hz), a criterion for ototoxic hearing loss was chosen that was far more conservative than other authors applied. Still, we found a high incidence of platinum ototoxicity. Several distinctions could be made with regard to the different patterns of ototoxicity of cisplatin and carboplatin, and with regard to age and preexistent hearing problems (risk factors).

First, this investigation showed a significant difference in patterns of ototoxicity between treatment with cisplatin 20 mg/m^2 for 5 consecutive days (group A), treatment with cisplatin 50 mg/m^2 by 4-hour infusions (group B), and treatment by carboplatin 350 mg/m^2 by half-hour infusions (group C).

In groups B and C, there were 42% and 25% undamaged ears, respectively, versus 9% undamaged ears in group A. In all three groups, ototoxic damage started mainly in the HF range and was restricted to this range in 33% to 41%. In group A, this HF onset turned into a BF loss in the final stage in 27%. This 27% represents a group of patients for whom HF audiometry can give a warning for further threatening hearing loss in the course of the treatment. As final hearing impairment, 48% of all ears (group A) developed a mainly or partially LF hearing loss, considering the final BF and LF groups together. This percentage should have been diagnosed as well with routine (250 to 8,000 Hz) audiometry.

In groups B and C, this HF onset loss became a BF loss in the final stage in 13% and 17%, respectively. Again, considering the final BF and LF groups together, 17% as compared to 33% of all ears developed a mainly or partially LF hearing loss in the final stage. In none of the three groups do the onset LF or BF hearing losses exceed 12% of all ears.

In spite of the small numbers of patients in groups B and C, the differences in patterns of ototoxicity are remarkable. The cisplatin 50 and, more modestly, the carboplatin 350 therapy seem to be preferable when ototoxic platinum treatment cannot be avoided.

Secondly, our HF material showed significant differences in the pattern of hearing loss related to age ($p<.001$). In patients up to 30 years of age, only 3% showed no damage after cisplatin 20 mg/m^2 treatment, whereas 90% developed HF onset damage. A BF hearing loss was the final result of this therapy in only 20% of all ears. In patients from 30 to 45 years of age, we recognized the same differentiation between no damage and HF onset damage, but BF final hearing deterioration was present in 60% of all ears. Truly, HF audiometry plays a predictive role for this group of patients.

In the oldest patient groups, the onset hearing loss was more localized in the LF and BF frequency ranges; in the final stage, there was no important difference between these oldest groups and the group 30 to 45 years of age, because together, the LF and BF final hearing deterioration amounted to about 70% of all ears. Obviously, with increasing age the ototoxicity pattern shifts to the LF range, in the onset as well as in the final stage of the platinum treatment.

Because of the strong relationship between age, sex, and type of tumor — younger males with testis tumors and older females with ovarian cancers — the ototoxicity pattern could not be identified for the different sexes.

Finally, in our results we traced the influence of former otologic problems on the patients' ototoxicity patterns. In the patient group with a troubled otologic history, there seemed to be a tendency to more hearing deterioration in the BF range.

In the near future, the authors hope to publish some detailed results of a study of the impact of the ototoxic changes in relation to drug dosage, especially in the HF range.

In this study, we only incidentally had to recommend termination of platinum therapy. Although the clinical consequences in this particular investigation were limited, we used HF audiometry to discover certain ototoxicity patterns. With this experience, we were able to develop a tool for early detection and monitoring of ototoxic damage, which also can be caused by recently introduced high dose cytostatic treatments and other experimental chemotherapeutic treatments.

We would recommend a reconsideration of the patient's cytostatic treatment in case of progression of an HF hearing loss (10,000 to 18,000 Hz) toward the LF range (≤8,000 Hz). In this respect, we plan to study the possibility of changing a cisplatin 20 mg/m^2 treatment, which proved to be more ototoxic in this study, into a cisplatin 50 mg/m^2 or carboplatin 350 mg/m^2 treatment.

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DEPRESSION OF T CELLS IN BELL'S PALSY

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We analyzed T-lymphocytes and their subsets in 20 patients with Bell's palsy. We used the monoclonal antibodies anti-Leu-1, anti-Leu-2a, and anti-Leu-3a directed against T-lymphocytes and T suppressor/cytotoxic (T_s) and T helper/inducer (T_h) cell subsets. Blood samples taken in the acute and convalescent phases of the illness were compared. The percentage of T cells (Leu-1^+ cells) was decreased during the acute stage, mainly because of a reduction of the T_h cell subset (Leu-3^+ cells). No significant alteration was found in the T_s cell subset (Leu-2^+ cells). The T cell and T_h cell subset depressions were restored to normal within 4 to 6 weeks of the onset of the palsy. The T cell changes in the peripheral blood in the acute stage of Bell's palsy indicate the involvement of cellular immune mechanisms.

KEY WORDS — Bell's palsy, T cells, T cell subsets.

INTRODUCTION

Acute peripheral facial palsy may have several causes, but in most cases the cause is unknown and the illness is called Bell's palsy. Vascular disturbances, viral infections, and an immunologic dysfunction have been suggested as possible causes.[1-3]

Lymphocytes from patients with Bell's palsy show, in vitro, a response to peripheral nerve P_1L basic protein. A similar response of the lymphocytes also has been demonstrated in patients with Guillain-Barré syndrome.[4] A cell-mediated autoimmune mechanism, probably postinfectious, was suggested, therefore, as an important factor in the pathogenesis of the paralysis in these two disease processes. In recent studies of the cellular immune response in Bell's palsy, a decrease in the T-lymphocytes of peripheral blood was reported during the acute stage of the disease.[2]

This study is part of an extensive investigation of the humoral and cellular immune response in patients with Bell's palsy. The aim of the present study was to evaluate the T cells and T helper/inducer (T_h) and T suppressor/cytotoxic (T_s) cell subsets in peripheral blood in the acute and convalescent stages in patients with Bell's palsy in an attempt to acquire further knowledge of the cause of the disease.

MATERIAL AND METHODS

PATIENTS AND CONTROLS

Twenty patients with Bell's palsy (nine females and 11 males) between 5 and 81 years of age (mean, 38 years) were studied during the period September 1984 to October 1985. All of the patients were examined first within 14 days (mean, day 7) after the onset of palsy. The patient's history was obtained, and an otoneurologic examination performed. The function of the facial nerve was classified according to the grading system (grades I through VI) proposed by House.[5] Pregnant women and patients with diabetes mellitus or malignant disease were excluded. None of the patients had bilateral palsy, had a history of recurrent disease, or was receiving steroid treatment. Neurological evaluation and follow-up studies were carried out by the same investigator (L.J.).

Thirty healthy blood donors between 18 and 40 years of age (mean, 30 years) were used as controls.

ROUTINE LABORATORY TESTS

Sedimentation rate, hemoglobin estimation, leukocyte counts, lymphocyte percentages, and thrombocyte counts were analyzed in blood taken in the acute phase (days 1 to 14; mean, day 7). Leukocyte counts and lymphocyte counts and percentages also were analyzed in the convalescent phase (days 19 to 81; mean, day 44) and/or during the phase of remission (5 to 17 months; mean, 12 months).

IMMUNOENZYMATIC STAINING

Peripheral blood lymphocytes were isolated from heparinized blood taken in the acute, convalescent, and remission stages by centrifugation on Ficoll-Isopaque followed by treatment with carbonylated iron powder. The cells then were fixed on slides with paraformaldehyde as previously described.

Immunoenzymatic staining was performed by sequential incubations with monoclonal antibody, biotinylated horse anti-mouse IgG, a complex of avidin and biotinylated horseradish peroxidase H (Vectastain, Kemila, Stockholm), and finally with a carbazol-containing buffer. No staining was observed when the primary antibody was omitted.[6,7]

The monoclonal antibodies used for detecting cellular antigens were purchased from Becton Dickinson (Stockholm). Anti-Leu-1 detects all T cells;

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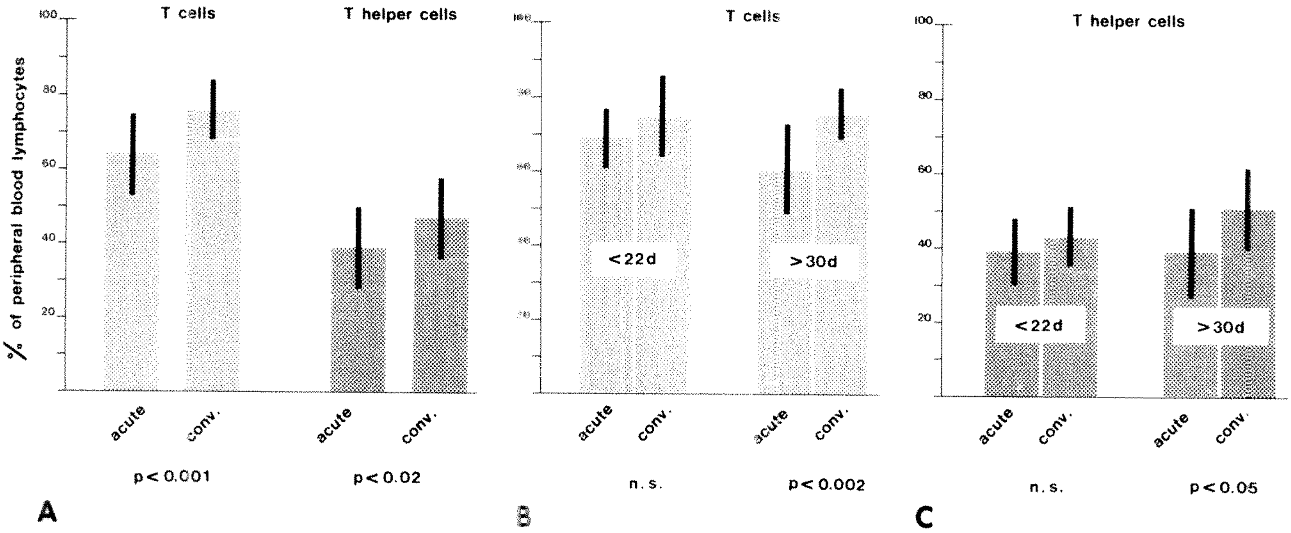

Percentages of T cells and T helper cells in peripheral blood from patients with Bell's palsy. A) Comparison of acute and convalescent (conv.) stages of palsy (n = 20). B) Interval between taking blood from patients in acute and convalescent stages < 22 days (n = 8) and > 30 days (n = 11). C) Interval between taking blood from patients in acute and convalescent stages < 22 days (n = 8) and > 30 days (n = 11).

anti-Leu-2a, T_s cells; and anti-Leu-3a, T_h cells. The antibodies were used in a dilution of 1:20.

STATISTICAL ANALYSIS

Student's unpaired *t* test was used for comparing patients and controls, and Student's paired *t* test was used for comparing patient values in the acute and convalescent or remission stages.

RESULTS

CLINICAL OUTCOME

All nine patients with incomplete palsy recovered entirely. Six of the 11 patients with complete palsy also recovered entirely. Four of the other five patients with complete palsy still have mild dysfunction (grade II), and one has moderate dysfunction (grade III). The five patients with sequelae have been followed up for 5 to 17 months (mean, 14 months). Thus, complete recovery was seen in 15 of 20 patients (75%). The mean time for complete recovery in the nine patients with incomplete palsy was 4.5 weeks (range, 3 to 10 weeks), and in the six patients with complete palsy, 2.7 months (range, 3 weeks to 6½ months).

ROUTINE LABORATORY TESTS

One patient had a transient elevation of the sedimentation rate (25 mm), and another had a transient thrombocytosis (450 x 10^9/L). One patient was referred to the Department of Medicine because of persistent thrombocytosis (800 x 10^9/L). The leukocyte counts, lymphocyte counts, and percentages of lymphocytes in the acute stage were not significantly different from those in the convalescent and remission stages. The mean level of peripheral blood lymphocytes was 2.0 x 10^9/L, and the mean lymphocyte percentage was 33%. These figures did not differ from the control values.

LYMPHOCYTE SUBPOPULATIONS

Patients With Incomplete and Complete Palsy (All Patients). The percentage of T cells (Leu-1^+) was lower in 18 of the 20 patients in the acute phase than in the convalescent phase. The corresponding values for the T_h (Leu-3^+) and T_s (Leu-2^+) cell subsets were 14 of 20 and 11 of 20, respectively. The percentage of T cells was decreased ($p < .001$) during the acute phase (mean ± SD, 64% ± 11%) compared with the convalescent phase (76% ± 8%) (see Figure, A). The acute depression of T cells was due to a decrease to the T_h cell subset (39% ± 11% versus 47% ± 11%, $p < .02$), whereas the percentage of the T_s cell subset was unchanged (31% ± 10% versus 33% ± 14%). The T cell and T_h cell subset values were normal in the convalescent stage as compared with the control values, which were 76% ± 8% for T cells, 49% ± 6% for T_h cells, and 29% ± 9% for T_s cells.

The peripheral T cell balance, defined by the T_h:T_s cell subset ratio, was lower in the acute phase (1.4 ± 0.5) than in the convalescent phase (1.9 ± 2.0), but the difference was not significant. The acute T_h:T_s cell subset ratio, however, was significantly lower ($p < .01$) than that of the healthy controls (1.3 ± 0.6).

The time interval for the recovery of the depression of T cells to the normal value also was scrutinized. The percentage of T cells was 69% ± 8% in the acute stage in those patients (n = 8) from whom blood was taken less than 22 days after the sample of the acute phase and the percentage of T cells was 75% ± 11% in the convalescent phase. This difference was not of statistical significance (Figure, B). In the 11 patients from whom blood samples were taken more than 30 days after the sample of the acute phase, however, the percentage of T cells was 76% ±7% in the convalescent phase, whereas that in the acute phase was 61% ± 12%. This was a significant difference ($p < .002$).

Regarding the Th cells, similar results were obtained (Figure, C). In the eight patients, the percentage was 39% ±9% in the acute stage; and in corresponding samples taken less than 22 days later, the percentage was 42% ±8%. The difference was not statistically significant. However, in samples taken at more than a 30-day interval, the percentage in the convalescent phase was 51% ± 11%. This difference was statistically significant ($p < .05$) compared with the percentage of 39% ±12% in the acute stage. Thus, the percentages of T cells and Th cells had returned to normal 4 to 6 weeks after the onset of palsy.

Patients With Incomplete Palsy. In the nine patients with incomplete palsy, there was a significant decrease ($p < .01$) in T cells during the acute stage (63% ±9%) compared with the convalescent phase (77% ±7%). The Th cell subset percentage also was lower in the acute stage (37% ±9% versus 44% ± 11%), but the difference was not statistically significant. Alteration of the Ts cell subset percentage (acute, 30% ±8%; convalescent, 29% ±9%) was not found.

Patients With Complete Palsy. A significant acute depression ($p < .05$) of T cells was seen also in the 11 patients with complete palsy (65% ±12% versus 75% ±10%). The corresponding values for the Th cell subset percentage were 40% ± 12% versus 49% ±9%, but this difference was not significant. No significant alteration of the Ts cell subset was found (31% ±12% versus 37% ±17%).

The five patients with complete palsy and sequelae showed the same pattern of T cell and Th cell subset changes (ie, lower values in the acute phase), but the depression was not significant. The six patients with complete palsy who recovered had a significant depression ($p < .02$) of T cells in the acute stage compared with the convalescent stage. An acute depression of the Th cell subset, although not significant, was seen also in these six patients. No alteration of the Ts cell subset was found in the two subgroups with complete palsy.

DISCUSSION

This study shows that there is an immunologic imbalance of the peripheral blood cells during the acute phase of Bell's palsy with a transient decrease in T-lymphocytes. This accords well with earlier reports.[2,8] Aviel et al,[2] however, reported a longer period (61 to 100 days) than we found (4 to 6 weeks) for restitution of the percentage of the T cell depletion. According to Manos-Pujol et al,[8] the decrease in the percentage of T cells in the acute stage was caused mainly by a depression of the Ts cell subset in patients with their first attack of facial palsy. The Th cell subset seemed to have a variable value, but the peripheral T cell balance (Th:Ts) was increased in the patients with their first attack. These results of the T cell subsets are in contrast to our own findings, namely a decrease in the Th cell subset and the Th:Ts cell ratio in the acute stage of the disease.

In the present investigation, only the peripheral blood cells were studied; therefore, the pattern of cell changes in the probable main target organ (the facial nerve) cannot be assessed. The T cell depression in blood may be caused by a decrease in the total amount of these cells in the body or, alternatively, by their redistribution.

The patterns of T cell and Th cell subset changes in patients with incomplete and complete palsy resembled each other. Both groups showed a significant depression of T cells during the acute phase compared with the convalescent phase. The Th cell subset depression was not significant, probably because of the small number of patients in the two groups. The patients with complete palsy and sequelae showed the same general pattern of T and Th cell changes as patients with incomplete palsy and those with complete palsy without sequelae. The five patients with sequelae, however, were probably too few to achieve significance in the T cell changes. These findings indicate that neither the severity nor the final outcome of the palsy can be predicted by the acute T cell changes. This is in accordance with earlier findings.[2] Our results also indicate that the outcome cannot be predicted by the acute Th cell subset change, nor by analysis of the Ts cell subset.

It has been speculated that a cell-mediated mechanism following an infection is an important factor in the pathogenesis of Bell's palsy.[4] The herpesvirus group has been suggested to be such an infectious cause.[3,9,10] Acute T cell changes also have been reported in diseases caused by these viruses. Both acute Epstein-Barr virus–induced and cytomegalovirus-induced types of mononucleosis have been associated with a decrease in the percentage of the Th cell subset and a corresponding decrease in the Th:Ts cell ratio.[11,12] Furthermore, cytomegalovirus seropositive blood donors have significantly lower Th:Ts cell ratios than do seronegative individuals, suggesting that the impact of cytomegalovirus infection on the immune system may be of longer duration.[13]

The T cell population also can be affected by another group of viruses, namely the retroviruses. These reverse transcriptase–containing viruses exist in two forms, exogenous and endogenous.[14] The known exogenous retroviruses infecting humans are the human T cell lymphotropic viruses (HTLV).[15] Suppression of T cells is most conspicuous after infection by the acquired immune deficiency syndrome (AIDS)–associated retrovirus human immune deficiency virus (HIV). It is now clear that humans also harbor endogenous retroviral sequences integrated in the DNA.[16,17] A connection between retrovirus infection and neurologic disorders was presented recently: AIDS-associated retroviruses have been isolated from the CSF and brain of patients with neurologic symptoms.[18] Data have been presented suggesting that some patients with multiple sclerosis respond immunologically to, and have CSF T cells containing a retrovirus related to but distinct from, the three types of HTLV.[19]

Resemblances between the findings in patients with Bell's palsy and those with other neurologic diseases have been outlined. Elevated myelin basic protein levels in the CSF in relation to pathologic auditory brain stem responses in patients with Bell's palsy[20] may support the view that in many cases it is a demyelinating disease confined to the brain stem, similar to multiple sclerosis. Furthermore, a T-lymphocyte depression is seen in peripheral blood in acute attacks of multiple sclerosis. In contrast to our findings in Bell's palsy, an increased Th:Ts cell ratio with a depression of the Ts cell subset has been reported in the acute stage of multiple sclerosis.[21,22]

Similarities in the cellular immune response to peripheral nerve basic protein in patients with Bell's palsy and patients with Guillain-Barré syndrome have been reported.[4] Furthermore, Lisak et al[23] found a decrease in the circulating Th cell subset with a decrease in the Th:Ts ratio in the acute phase in three of 13 patients with Guillain-Barré syndrome. These facts may tempt one to speculate that there are subgroups of Guillain-Barré syndrome, one of them with the only obvious neurologic dysfunction being Bell's palsy.

In conclusion, we have found a decrease in peripheral blood T-lymphocytes due mainly to a depression of the Th cell subset during the acute stage of Bell's palsy. A transient immunodeficiency with a Th cell subset depression may be an important cause in the pathogenesis of the palsy. One may wonder if this deficiency is caused by a primary virus infection, or if there is another immune mechanism leading to the Th cell deficit, which in turn may enable latent viruses to become reactivated.

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Ann Otol Rhinol Laryngol 97:1988

PROSPECTIVE STUDY OF THE EFFECTS OF VENTILATION TUBES ON HEARING AFTER RADIOTHERAPY FOR CARCINOMA OF NASOPHARYNX

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In patients with nasopharyngeal carcinoma, deafness sometimes occurs following radiotherapy. It is usually conductive, but may be sensorineural. Tinnitus is present frequently and usually is distressing. The role of ventilation tubes (grommets) in relieving these problems was assessed in a prospective randomized controlled trial of 115 patients. In the group with grommets, there was an improvement in hearing, with a reduction of the averaged air-bone gap ($p < .01$). This was not found in the control group without ventilation tubes, who developed a larger conductive loss ($p < .01$) and, in addition, a slight deterioration of the averaged bone conduction threshold ($p < .01$). Surprisingly, the group with grommets did not develop this sensorineural loss ($p > .01$). In addition, tinnitus was improved significantly by the insertion of ventilation tubes ($p < .01$). Neither necrosis nor stenosis of the external auditory meatus was found in either group.

KEY WORDS — hearing loss, nasopharyngeal carcinoma, radiotherapy, ventilation tubes.

INTRODUCTION

Radiotherapy (RT) in the treatment of a malignancy of the postnasal space may have some effects on hearing. Most investigators agree that there can be a conductive loss resulting from alterations in eustachian tube function or from soft tissue changes caused either by the tumor or occurring as a side effect of the RT.[1,2] The insertion of a ventilation tube theoretically should overcome the eustachian tube dysfunction and improve hearing. To the best of our knowledge, however, there are no controlled prospective studies showing this effect, although the procedure is widely practiced.

Development of a sensorineural hearing loss following RT is also likely, since experimental results in guinea pigs showed destruction of the organ of Corti following a large single dose of external radiation.[3] In clinical practice, destruction of the human organ of Corti also has been seen in temporal bones of patients who had received RT.[4,5] Clinicians are not always convinced, however, that this occurs with conventional treatment schedules. Dias,[6] Borsanyi et al,[7] and Thibadoux et al[8] felt that sensorineural hearing loss either did not occur or was only a minor problem. On the other hand, Leach[4] and Moretti[9] felt that this form of hearing loss was really quite common following temporal bone irradiation, and that it might be delayed in onset. Prevention of sensorineural hearing loss would not be expected following the insertion of ventilation tubes in the tympanic membrane; consequently, there are no studies related to this.

The aim of this study was threefold: 1) to perform a prospective controlled trial to assess the effects of ventilation tube insertion on the incidence of conductive hearing loss following RT that included the temporal bone; 2) to determine whether sensorineural hearing loss did occur following such RT, and if the insertion of ventilation tubes had any protective effect on it; and 3) to evaluate whether tinnitus was present before, developed during, or was made worse by RT, and if it was, to assess whether ventilation of the middle ear had any effect on its severity.

MATERIALS AND METHODS

Between March 1984 and July 1985, 115 patients were entered into the trial. All were new cases diagnosed as having nasopharyngeal carcinoma by Unit A of the Medical and Health Department Institute of Radiology and Oncology at Queen Elizabeth Hospital, Hong Kong. Only those patients with disease in stages I through IV (Ho's classification of 1978[10]) were included.

All cases were seen prior to RT and were assigned randomly to ventilation tube (T) or no ventilation tube (NOT) groups. Then they were seen at the Ear, Nose, and Throat Clinic, British Military Hospital, Hong Kong, by one of the authors (C.R.C.), and those with symptomatic ear disease or congenital anomalies were excluded. At the end of this procedure, there were 58 patients in the T group and 57 in the NOT group, with no major difference in the distribution of staging levels between the groups (Table 1). At the first visit, patients were asked about deafness, earache, otorrhea, tinnitus, and dizziness. Reports of relevant nose and throat symptoms also were elicited. Each patient's ears were examined to exclude the asymptomatic presence of ex-

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TABLE 1. DISTRIBUTION OF PATIENTS

	T	*NOT*
Number	58	57
Median age	52 yr	52 yr
Range	26-77 yr	26-73 yr
Men	40	44
Women	18	13
Stage I	12	10
Stage II	9	12
Stage III	14	13
Stage IV	23	22

Tumor staging system is that of Ho.[10]

T — ventilation tube, NOT — no ventilation tube.

ternal otitis or chronic suppurative otitis media. In addition, the cranial nerves were tested and the nose and throat were examined.

A pure tone audiogram using a Kamplex AC3 audiometer (P. C. Werth, London) was performed in a soundproof booth by an experienced technician. A Madsen (Buffalo, NY) tympanoscope Z5330 was used to produce a tympanogram.

At this first visit and prior to RT, the T group had Shepperd's grommets inserted in both tympanic membranes under local anesthetic (Citanest with Octapressin, Astra Pharmaceuticals). All patients were given a follow-up appointment 3 months later, which was approximately 6 weeks after completion of RT.

The RT schedule consisted of 6,000 cGy delivered in 24 fractions over 6 weeks from a 4.5–mega electron volt linear accelerator to the nasopharynx. The fields included the temporal regions within the target volume, and if there was cervical node involvement, the neck also was irradiated.

At the follow-up visit to the Ear, Nose, and Throat Clinic, the history, examination, and investigations were repeated, except that the T group did not have tympanometry. This procedure was repeated at 3-month intervals, and in this paper we present results up to 6 months, although longer-term follow-up continues.

ANALYSIS OF DATA

The pure tone audiograms were assessed in two ways. First, the averaged air-bone gap of 250 and 500 Hz was calculated at the first visit and at the 3-month visit. Second, the sensorineural threshold was determined as the averaged masked bone conduction level at 2, 4, and 6 kHz at the first visit and then at the 6-month visit. The air-bone gap was not assessed at 6 months, as during the 3- to 6-month period a number of ventilation tubes were expelled from the tympanic membrane. To assess whether the two groups (T and NOT) were equivalent at the start of the trial, the mean air-bone gap of the T group was compared with that of the NOT group using a Student's *t* test. The same procedure was performed for the averaged sensorineural threshold. The effects of RT then were assessed using a paired *t* test within each group to compare the value of the air-bone gap or the sensorineural threshold before and after RT. Finally, the audiometric data from the two groups after treatment were assessed again by Student's *t* test to determine whether there were differences between the T and NOT groups with regard to the mean air-bone gap and the mean sensorineural threshold.

TABLE 2. MEAN AIR-BONE GAP

	T	*NOT*
Number	106	101
0 months	19 dB	21 dB
Student's *t* test: $t = 1.62$, $p = .1$		
3 months	12 dB	24 dB
Paired *t* test	$t = 9.1$ $p < .001$	$t = 3.2$ $p < .01$

The tinnitus was assessed by asking whether the patient had tinnitus or not, and if it was present, whether it was mild or severe. The answers were graded as 0 = absent, 1 = mild, and 2 = severe. The resulting figures were analyzed in a fashion similar to that used for the audiometric data.

For a variety of reasons, not all patients could be followed up, so that both the tinnitus and sensorineural threshold results are given only for those patients who completed the 6-month follow-up. There were 78 ears in the T group and 81 ears in the NOT group. More patients were seen at the 3-month follow-up, and again the data related to the air-bone gap are presented only for those who were followed in this time period (106 ears in the T group and 101 ears in the NOT group). The number of ears is not twice the number of patients, as several patients had a severe or profound unilateral sensorineural loss before treatment, and the affected ears were excluded.

RESULTS

When the air-bone gaps of the two groups prior to treatment are compared, there is no significant difference between the two populations that have a mean air-bone gap of around 20 dB (Table 2). The average sensorineural threshold is 25 dB (Table 3), and again there is no significant difference between the two groups.

The conductive hearing loss present before treatment increased by 3 dB in the NOT group, whereas the hearing improved by 7 dB in the T group (Table 2). These were significant findings.

A small decrease of 3 dB in the averaged sensorineural threshold occurred at 6 months in the NOT

TABLE 3. BONE CONDUCTION THRESHOLD AT 0 MONTHS

	T	*NOT*
Mean bone conduction threshold	25 dB	25 dB
Number	78	81
Student's *t* test: $t = 0.609$, $p = .5$		

TABLE 4. MEAN LEVEL OF SENSORINEURAL THRESHOLD

	T	*NOT*
0 months	25 dB	25 dB
6 months	24 dB	28 dB
Paired t test	$t = 1.36$ $p > .1$	$t = 5.79$ $p < .001$

group. This hearing loss was not found in the T group. Again, these findings were statistically significant, although the average loss was slight (Table 4). When individual data were analyzed, it was apparent that some patients suffered a marked worsening of their bone conduction threshold. There were five patients with losses greater than 10 dB in the NOT group and three in the T group, but the small number precluded statistical analysis.

The groups did not differ with regard to tinnitus scores (Table 5) at the beginning of the trial. By the end of 6 months the NOT group had significantly worse tinnitus, whereas the T group showed a marked and significant improvement. When the two groups were compared at the end of 6 months, the tinnitus scores were significantly different, with the NOT group having worse symptoms.

There were no cases of canal stenosis or necrosis in either group, and although a few patients developed external otitis or otitis media, there was no difference in the incidence between the two groups.

DISCUSSION

This prospective controlled trial confirmed earlier reports that a conductive hearing loss was present in some patients with nasopharyngeal carcinoma, and that this increased during a subsequent course of RT involving the nasopharynx and temporal region. Of the other patients who did not have an air-bone gap on presentation, some also developed a conductive hearing loss during treatment. The insertion of the ventilation tube had the expected effect of immediately relieving this distressing disability in those who had a middle ear effusion at presentation. It also appeared to prevent the occurrence of conductive hearing loss in those who did not have an effusion before treatment. Presumably, the RT or the tumor itself alters the eustachian tube function, resulting in a change in middle ear ventilation, and the ventilation tube reverses this process.

A small but definite sensorineural hearing loss developed in the NOT group following RT, although the averaged loss tended to hide those few people with more severe problems. Five individuals had an averaged sensorineural loss of greater than 10 dB. Surprisingly, the T group did not develop an overall sensorineural loss, although there were three individuals who by 6 months had more than 10 dB worsening of averaged thresholds. Why a sensorineural hearing loss developed is not clear, especially when a ventilation tube appeared to prevent it. Does the presence of fluid or negative middle ear pressure splint the ossicular chain and lead to an apparent sensorineural loss, as occurs in otosclerosis and manifests by the Carhart notch? This does not occur with ventilation tubes and would account for the failure of the sensorineural loss to develop. Whatever the precise mechanism of this protective effect, the outcome is clear, and perhaps an animal model could provide clues to explain this unexpected finding. In addition, temporal bone studies of patients who have died of nasopharyngeal carcinoma, both treated and untreated, should be performed where possible, to assess the effect of present-day RT on the human cochlea.

TABLE 5. MEAN TINNITUS SCORE

	T	*NOT*
Number	53	50
0 months	0.6	0.5
Paired t test	$t = 0.96$	$p > .3$
6 months	0.2	1.0
Paired t test	$t = 7.6$	$p < .001$
Mean difference, 0 months and 6 months	+0.4	−0.6
t value	+4.1 $p < .001$	−4.7 $p < .001$

Tinnitus score less after treatment (+) or more after treatment (−).

Tinnitus may arise from negative pressure or from fluid in the middle ear, as well as from changes in the cochlea. The significant reduction in tinnitus in the T group could therefore be explained by any of these factors' being relieved or prevented. Although tinnitus is difficult to measure objectively, and no attempt to do so was made in this study, the patients' symptoms were improved significantly by this simple procedure, which had minimal complications.

We hope to continue this study to evaluate the long-term benefits of middle ear ventilation during RT.

CONCLUSION

With the advent of improved RT techniques and diagnosis of nasopharyngeal carcinoma at an early stage, more patients become disease-free. Even those who are not cured often remain symptom-free and survive longer than in the past. Many of them suffer from a distressing tinnitus, a hearing loss, or both. The insertion of middle ear ventilation tubes under local anesthetic prior to RT significantly reduces the incidence and severity of these additional problems, with minimal complications. We therefore recommend that the insertion of ventilation tubes in these patients should be a routine procedure prior to RT in order to improve the quality of their lives.

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EUROPEAN RHINOLOGIC SOCIETY

The European Rhinologic Society will hold its 12th Congress with the ISIAN meeting June 19-22, 1988, in Amsterdam. On June 23-25, 1988, a course in nasal and sinus surgery will be held in Utrecht. For further information, contact Prof Dr E. H. Huizing, Dept of Otorhinolaryngology, University Hospital Utrecht, PO Box 16250, 3500 CG Utrecht, The Netherlands.

Ann Otol Rhinol Laryngol 97:1988

AUDITORY AND VESTIBULAR DISORDERS DUE TO BAROTRAUMA

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In order to investigate auditory and vestibular disorders caused by barotrauma, 12 guinea pigs were exposed to compression and decompression between 1 absolute pressure (ATA) and 2 ATA in a pressure chamber. During the atmospheric pressure change, spontaneous nystagmus occurred in two thirds of the animals. Auditory dysfunction that showed the difference between the right and left ears was confirmed by auditory brain stem response and Preyer's reflex in the animals with spontaneous nystagmus. Damage to the organ of Corti was the most significant cause for the auditory dysfunction. Though findings attributed to the rupture of the round window membrane were recognized in four ears, the rupture or hemorrhage of the round window membrane was not the direct cause of the auditory dysfunction. The significance of the round window membrane rupture is discussed.

KEY WORDS — auditory evoked potentials, barotrauma, nystagmus, Preyer's reflex.

Because of the recent increase in the frequency of aircraft travel and the popularity of scuba diving, more individuals are exposed to large variations in atmospheric pressure.[1,2] Variations in atmospheric pressure occasionally lead to decompression sickness or aural barotrauma resulting in auditory and vestibular disorders. Decompression sickness is related to bubble formation in the bloodstream as pressure drops below the level required to keep gas soluble. Decompression sickness is a general disorder that is unrelated to auditory tube function. On the other hand, the cause of aural barotrauma is the difference between the pressure of the middle ear (ME) and that of the external or inner ear. In barotrauma of the ME or barotitis media, vascular engorgement, bleeding, and formation of exudate in the middle ear space are seen. Inner ear barotrauma causing perceptive hearing loss or vertigo also has been reported.[3] Recently there have been many clinical reports of labyrinthine window rupture following the atmospheric pressure change. The labyrinthine window ruptures noted in divers in all but two cases[4,5] thus far reported have been round window ruptures, whereas oval window ruptures are more common in non-diving-related labyrinthine ruptures.[6,7] In cases of labyrinthine window ruptures, both auditory and vestibular impairments usually exist,[8] but the clinical manifestations of the labyrinthine window ruptures are varied. There are cases of only auditory or only vestibular impairment. There are even some cases with neither hearing loss nor vertigo.[9,10] The reason for the variability of the manifestations is obscure. The variability may be attributed to differences in the conditions inside the inner ear. Simmons[11] postulated that rupture of Reissner's membrane or the basilar membrane can occur following the labyrinthine window rupture due to barotrauma, with subsequent occurrence of auditory and vestibular dysfunction. The postulated pathophysiology of inner ear injuries related to altered atmospheric pressure exposure has not been well demonstrated, however.

There have been several experimental reports describing the changes of the inner ear following atmospheric pressure change using a hyperbaric pressure chamber on rabbits,[12] cats,[13] guinea pigs,[14-17] rats,[18] and monkeys.[19] In these experiments, the mode of compression and decompression varied a great deal, depending on whether the purpose was to investigate decompression sickness or aural barotrauma. In some of these experiments, the ME space was opened artificially by perforating the tympanic membrane or opening the tympanic bulla before the pressure loading in order to eliminate aural barotrauma and study pure decompression sickness. In two experiments that were attempted to cause aural barotrauma in guinea pigs, the rupture of the round window membrane occurred;[15,17] however, these two reports did not describe the state of Reissner's membrane. We attempted to cause aural barotrauma in guinea pigs and observe the resultant functional and morphologic changes, including changes in Reissner's membrane and the basilar membrane.

METHODS

Twelve white guinea pigs weighing 150 to 300 g were exposed to changes in atmospheric pressure. The animals were put in a pressure chamber in which a pressurized oxygen infusion elevated the atmospheric pressure up to 2 absolute pressure (ATA) in 3 minutes and maintained it at that pressure for 10 minutes. Then the chamber gas outlet was opened

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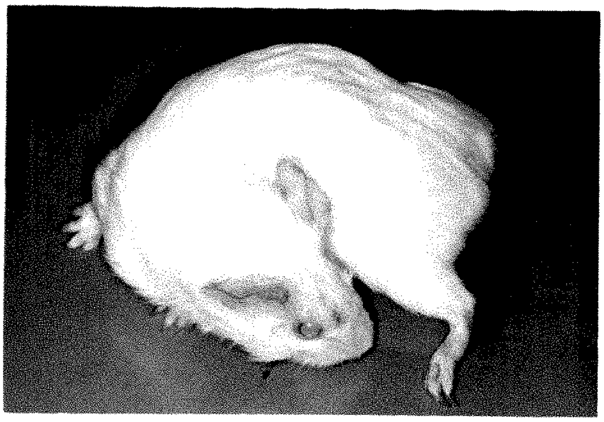

Fig 1. Guinea pig that had spontaneous nystagmus during atmospheric pressure change. Animal showed horizontal nystagmus to right and rotated in counterclockwise direction.

so as to decrease the atmospheric pressure from 2 ATA to 1 ATA in 30 seconds. At the pressure level of 2 ATA, the volume percent of oxygen and nitrogen were about 60% and 40%, respectively. The chamber had two windows through which the movements of the animals could be observed. The direction and duration of the spontaneous nystagmus caused by the pressure change were investigated. A rotatory test, a test of Preyer's reflex (acoustic pinna reflex), and an auditory brain stem response (ABR) test were performed in all animals both before and from 24 to 48 hours after their exposure to the pressure change.

In the rotatory test, electronystagmograms were obtained without anesthesia using an electric turntable. After the animals were wrapped and their eyes were covered to avoid visual suppression, electronystagmograms were obtained using needle electrodes inserted near the external canthi of both eyes. Postrotatory nystagmus (PRN) was induced by abruptly stopping the turntable after turning the animals clockwise or counterclockwise. Clockwise and counterclockwise rotations were carried out alternately at intervals. The speed of the rotations was six or eight revolutions in 20 seconds. Directional preponderance of the nystagmus was investigated by comparing the occurrence and duration of the nystagmus to the right with those of nystagmus to the left under the same speed of clockwise and counterclockwise rotations. This comparison was made four times by performing four trials before and after the pressure loading, respectively.

The threshold of Preyer's reflex was measured using a PA audiometer (Nagashima). The audiometer was set up for the evaluation of Preyer's reflex and had a testing box in which the animals were put. The testing box had a windowpane through which the movements of the pinnas were observed. A speaker was mounted on the top of the testing

EFFECTS OF ALTERATIONS IN ATMOSPHERIC PRESSURE

Animal	*Spontaneous Nystagmus, Direction of Fast Component and Duration*	*Percentage of Asymmetry of Postrotatory Nystagmus**	*Change in Preyer's Reflex (Degree of Impairment)*	*Elevation of Threshold of ABR (dB)*	*Middle Ear Hemorrhage*	*Damage to Organ of Corti*
1	None	LDP 27(3)/LDP 33(11)	None	R 0 L 0	— —	No No
2	R, 6.0 min	LDP 4(10)/RDP 2(11)	Asymmetry (R<L)	R 15 L 40	+ + +	Yes Yes
3	None	LDP 1(6)/RDP 1(4)	None	R 0 L 0	+ +	No No
4	R, 3.0 min	LDP 7(5)/RDP 5(6)	Asymmetry (R<L)	R 0 L 30	+ +	No† Yes†
5	R, 2.5 min	RDP 5(6)/LDP 12(14)	Asymmetry (R<L)	R 0 L 30	+ + +	No Yes
6	R, 0.5 min	LDP 6(6)/0(7)	Asymmetry (R<L)	R 0 L 30	+ + +	No Yes
7	L, 2.0 min	LDP 13(11)/LDP 15(6)	Asymmetry (R>L)	R 5 L 0	+ + +	No No
8	L, 4.0 min	RDP 32(13)/RDP 16(3)	Total disappearance	R 70 L 40	+ + + + +	Yes Yes
9	L, 2.0 min	RDP 5(2)/RDP 6(5)	Asymmetry (R>L)	R 10 L 0	+ + + +	Yes No
10	None	RDP 5(4)/RDP 4(6)	None	R 0 L 0	+ +	No No
11	L, 2.5 min	LDP 7(4)/LDP 8(5)	Total disappearance	R 30 L 25	+ + + + +	Yes† Yes†
12	None	LDP 12(5)/LDP 18(10)	None	R 0 L 0	+ —	No No

ABR — auditory brain stem response; L — left; LDP — left directional preponderance; R — right; RDP — right directional preponderance; + indicates hemorrhage in part of mucous membrane of middle ear; + + indicates hemorrhage in almost all parts of mucous membrane of middle ear; + + + indicates blood clot formation with hemorrhage in almost all parts of mucous membrane of middle ear.

*After/before. Numbers in parentheses indicate standard deviation.

†Analyzed by H & E staining.

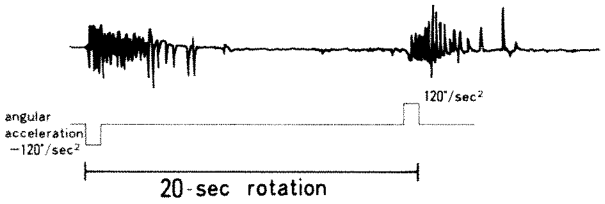

Fig 2. Nystagmus during and after rotation. Period of rotation indicated by horizontal line was 20 seconds. This example was recorded after pressure loading in guinea pig that had resultant spontaneous nystagmus.

box, and both right and left ears were stimulated simultaneously. The stimuli were 500-ms tone bursts of 500, 1,000, 2,000, 4,000, 8,000, 10,000, 12,000, and 15,000 Hz, respectively. The intensity of the stimuli was increased until clear movement of the pinna was obtained in each of the frequencies in both right and left ears, respectively. Moreover, the sizes of the movements of the right and left pinnas were compared at more intense stimuli. Before measuring the threshold of Preyer's reflex in the animals exposed to pressure loading, we compared the movement of the right pinna to that of the left pinna in Preyer's reflex after the unilateral external ear canal was plugged with cotton and glycerin in three guinea pigs for evaluation of the uncrossed reflex arc of Preyer's reflex. In these three animals, the difference of the movements between the right and left pinnas was observed in Preyer's reflex. The threshold of Preyer's reflex increased in both sides, but the degree of the elevation was stronger in the side on which the external ear canal was plugged than in the contralateral side.

The ABR was measured in a soundproof room where the dark noise level was about 30 dBA after intraperitoneal injection of 30 mg/kg Nembutal. All animals tolerated this temporary restraint well. Needle electrodes were inserted subcutaneously at the vertex and at subauricular regions near both external ear canals. As for the auditory stimulus, clicks were presented at a rate of 1 click/75 ms through an earphone inserted into a small speculum. The tip of the speculum was attached to the orifice of the external ear canal. Acoustic calibration was carried out by measuring the sound pressure level at the tip of the speculum. The animals were stimulated monaurally while masking sound was introduced into the contralateral ear through the similar speculum and earphone. Before the tests of ABR in animals exposed to pressure loading, ABR was performed in two guinea pigs in each of which one cochlea was destroyed surgically. The control experiment showed that the stimulus was transmitted to the contralateral ear with attenuation of about 40 dB when no masking was performed. The responses to 1,024 stimuli were averaged between the vertex and the stimulated ear by a signal processor (Sanei 7T17). The threshold and the latency of the ABR were evaluated.

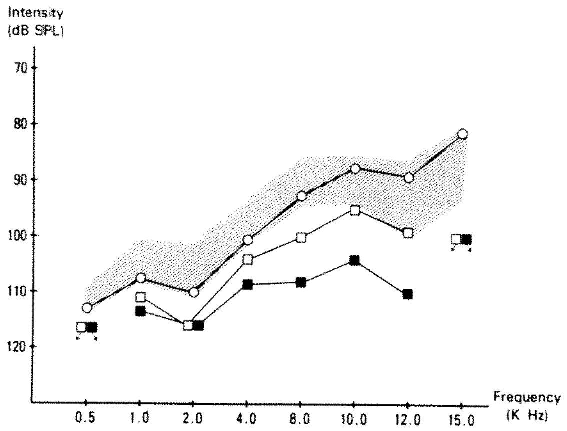

Fig 3. Example of asymmetric Preyer's reflex due to pressure loading in animal 5 in Table. Open circles — thresholds measured before exposure. Shaded area — ±1 SD from averages of thresholds measured in 12 guinea pigs before exposure. Before exposure, thresholds of right and left pinnas were same. Squares — thresholds after exposure. Open and closed squares — thresholds of right and left pinna, respectively. Arrows indicate scaling out.

At 48 hours after exposure to the pressure change, the animals were anesthetized deeply and decapitated. Then both right and left tympanic bullas were removed and opened. The state of the ME including the tympanic membrane and labyrinthine windows was observed using an operating microscope. Four ears were investigated serially using H & E staining. Other inner ears were analyzed by surface preparation technique for which the cochleas were fixed by 2% glutaraldehyde for 24 hours after the apical opening was made. After fixation, the cochleas were decalcified in 10% EDTA, an apicobasal section of the cochlea was made using a razor blade, and the state of the inner ear hemorrhage was observed by a stereomicroscope. The cochleas were then counterstained in 1% osmic acid, and the conditions of the Reissner's membranes were examined. After the cochleas were dissected under the stereomicroscope, the organs of Corti were examined by phase-contrast microscopy.

RESULTS

Following the atmospheric pressure change, spontaneous nystagmus occurred in eight of 12 animals. Under these experimental conditions, the spontaneous nystagmus began during decompression — not during compression or at 2 ATA. The animals that had spontaneous nystagmus turned their heads and rotated toward the direction of the slow component of the nystagmus (Fig 1). The fast component of the nystagmus moved toward the direction opposite to that of the rotation of the animals, ie, to the right in four animals and to the left in four animals (Table). The directions of the nystagmus were almost horizontal, but in two cases a rotatory component also was observed. The duration of the nystagmus ranged from 30 seconds to 6 minutes, after which no spontaneous nystagmus was observed again. When the animals were put back in their cages, all animals

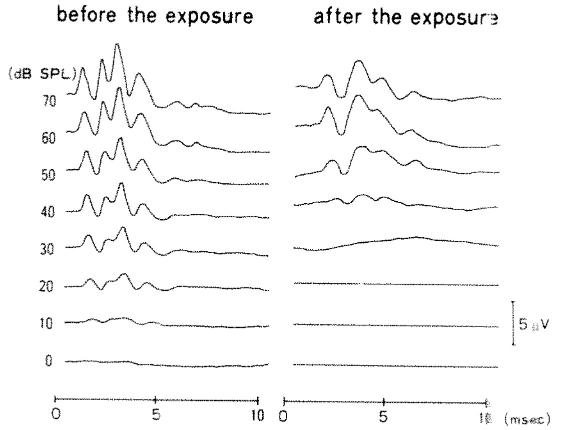

Fig 4. Example of ABR before and after exposure to pressure change showing elevation of threshold of 30 dB. Wave V was not clear, either before or after exposure.

showed normal gait, ordinary appetite, and no deviation of the body as judged from their appearance.

Regarding the rotatory test, Fig 2 shows an example of an electronystagmogram during and after rotation. Immediately after rotation, nystagmus began and was followed by a period of no nystagmus. After stopping the turntable, PRN in the opposite direction appeared. The directions of the fast component of PRN induced by stopping clockwise and counterclockwise rotation were left and right, respectively. Asymmetry of PRN was expressed as a percentage and calculated using the formula

$$\mathrm{PRN_{asymm}} = \frac{|\mathrm{PRN_r} - \mathrm{PRN_l}|}{\mathrm{PRN_r} + \mathrm{PRN_l}}$$

where $\mathrm{PRN_r}$ and $\mathrm{PRN_l}$ denote number of PRN to the right and left, respectively.

Asymmetry of PRN before and after pressure loading is shown in the Table. Asymmetry of PRN did not change significantly, even in animals that had spontaneous nystagmus on exposure to pressure change. One animal (animal 1) showed left directional preponderance, and one animal (animal 8) showed right directional preponderance, both before and after the exposure to the pressure change. Animals that showed directional preponderance of PRN also showed similar directional preponderance of per-rotatory nystagmus during rotation. Asymmetry of duration of PRN also did not change significantly on exposure to pressure change. In comparing the absolute number of the nystagmus induced by rotation on different days, the fact that natural variations may occur in the same animal on successive days should be taken into consideration.[20] In one animal, however (animal 11 shown in the Table), the number of both per-rotatory nystagmus and PRN decreased more than 50% following pressure loading.

Auditory dysfunction appeared in animals that had spontaneous nystagmus. The change of the threshold of Preyer's reflex was observed in eight animals. The Table also shows the change in Preyer's reflex at both right and left pinnas. In six animals, a difference in threshold between the right and left pinnas was observed (asymmetric Preyer's reflex). Figure 3 shows an example of an asymmetric Preyer's reflex. Asymmetric Preyer's reflex was more evident in higher frequency test signals.

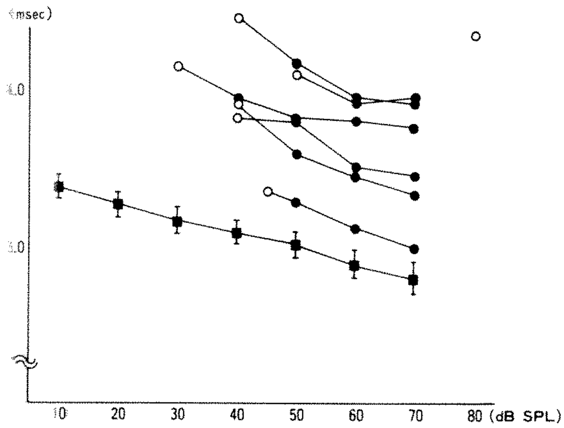

Fig 5. Changes of latencies of ABR due to barotrauma. Squares — average of latencies of wave III before exposure to pressure change in 24 ears of 12 animals. Vertical lines — ± 1 SD from mean. Before exposure, thresholds were ≤ 10 dB SPL in all ears. Circles — latencies of wave III in seven ears that showed elevation of threshold ≥ 30 dB after exposure. Open circles — thresholds of ABR. In one animal, threshold of ABR was 80 dB SPL after exposure. Thresholds increased and latencies prolonged after exposure.

With regard to the waveform of the ABR, waves I, II, III, and IV were clear, whereas wave V was not clear. Elevation of the threshold of ABR was recognized in 11 ears, as shown in the Table. Unilateral change of ABR was recognized in five, and bilateral change in ABR in three of eight animals that had spontaneous nystagmus.

Figure 4 shows an example of the elevated threshold of the ABR caused by exposure to pressure change. The auditory dysfunction was more evident in the ear toward which the slow component of the spontaneous nystagmus moved. The latencies of the waves were prolonged in ears that showed elevation of the threshold as shown in Fig 5. In 13 ears that did not show elevation of the threshold, the latencies were the same as those before exposure. There was a significant correlation between the results of the tests of ABR and Preyer's reflex. Elevation of the threshold of Preyer's reflex was observed in the ears in which the change in ABR was recognized.

Various degrees of hemorrhage in the ME were observed in 21 of 24 ears, as shown in the Table. There was a tendency for the auditory dysfunction to be stronger in the ears that had more hemorrhage in the ME space; but there was no clear correlation between ME hemorrhage and auditory dysfunction. For example, the right ear of animal 9, which had only a 10-dB elevation of the threshold of ABR,

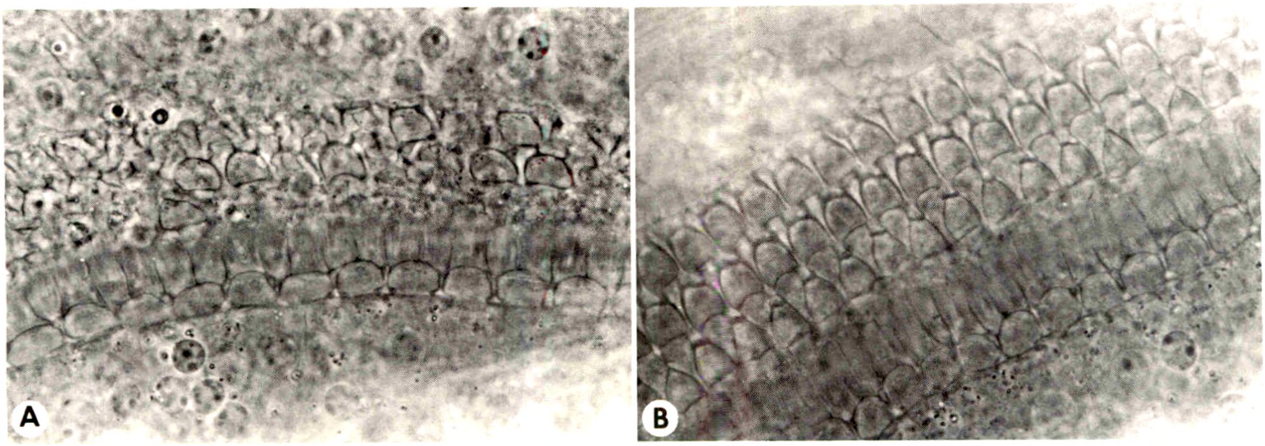

Fig 6. Organ of Corti demonstrated by surface preparation. A) Part of basal turn shows damage of outer hair cells of organ of Corti after pressure loading. Inner hair cells are normal. B) Part of second turn of same ear, showing normal organ of Corti, ie, three rows of outer hair cells and one row of inner hair cells. This ear had 30-dB elevation of threshold of ABR.

as shown in the Table, had the most severe hemorrhage in the ME space.

Injuries or degeneration of the organ of Corti were recognized in ten ears. Figure 6 shows an example of the damage to the organ of Corti demonstrated by the surface preparation technique. In all cases the outer hair cells sustained more damage than the inner hair cells. There was a tendency for the damage to be more pronounced in the basal end than in the upper turns, but the pattern of damage in different turns was complicated. Auditory dysfunction, investigated by tests of ABR and Preyer's reflex, had the most obvious relation to the damage of the organ of Corti (Table).

Inner ear hemorrhage occurred more frequently in the cochlea than in the semicircular canals, though the amount of the hemorrhage was less than that in the ME. Blood commonly was found in the scala tympani of the basal turn close to the round window, as shown in Fig 7A; however, a small amount of hemorrhage in the perilymph of the semicircular canals was seen (Fig 7B). There was no direct relationship between inner ear hemorrhage and auditory dysfunction.

Findings attributed to the rupture of the round window membrane were recognized in four ears. Occasional adhesion of blood clots to part of the round window membrane made it difficult to judge the presence or absence of ruptures. There was a tendency for the inner ear hemorrhage to be more severe in ears with rupture of the round window membrane; however, the round window membrane rupture did not necessarily occur in ears that showed auditory dysfunction. In animal 6, showing only unilateral elevation of the threshold of ABR (Table), the round window membrane rupture was recognized in only the contralateral ear, which showed no change in ABR. There was thus no direct relationship between the extent of auditory dysfunction and changes in the round window membrane.

Rupture of Reissner's membrane, the basilar membrane, the tympanic membrane, and the oval window could not be observed. In contrast to the damage to hair cells of the organ of Corti, no damage to cells of the stria vascularis, crista ampullaris, utricle, or saccule could be demonstrated by light microscopy.

DISCUSSION

We considered that the damage to the organ of Corti was the most significant cause of the auditory dysfunction in this experiment. It was thought that the pressure was transmitted to the organ of Corti, causing morphologic and functional damages. There have been several experimental reports describing damage to the organ of Corti following pressure loading. Hando et al[15] were able to produce inner ear barotrauma in guinea pigs by changing the atmospheric pressure from 1 ATA to 2 ATA within 4 minutes. They observed degeneration or disappearance of the sensory hairs, mainly in the outer hair cells, using a scanning electron microscope. They stated that the damage of the sensory hairs was noted immediately after the pressure loading in all cochlear turns, and that there was hardly any difference in the degree of damage in each turn. Tanabe et al[16] also observed the damage of the sensory hairs in inner ear barotrauma in guinea pigs, and stated that the damage of the hairs was noted mainly in the basal turn. Staining the hair cells with nitroblue tetrazolium, Takahashi[17] also reported the damage of inner ear hair cells due to barotrauma in guinea pigs. He stated that the basal turn sustained more damage than the apical turn, except in a few cases in which the apical or third turn was the most damaged.

We used a hyperoxic mixture in a hyperbaric pressure chamber in order to avoid nitrogen bubble formation in the bloodstream. Though this hyperoxic

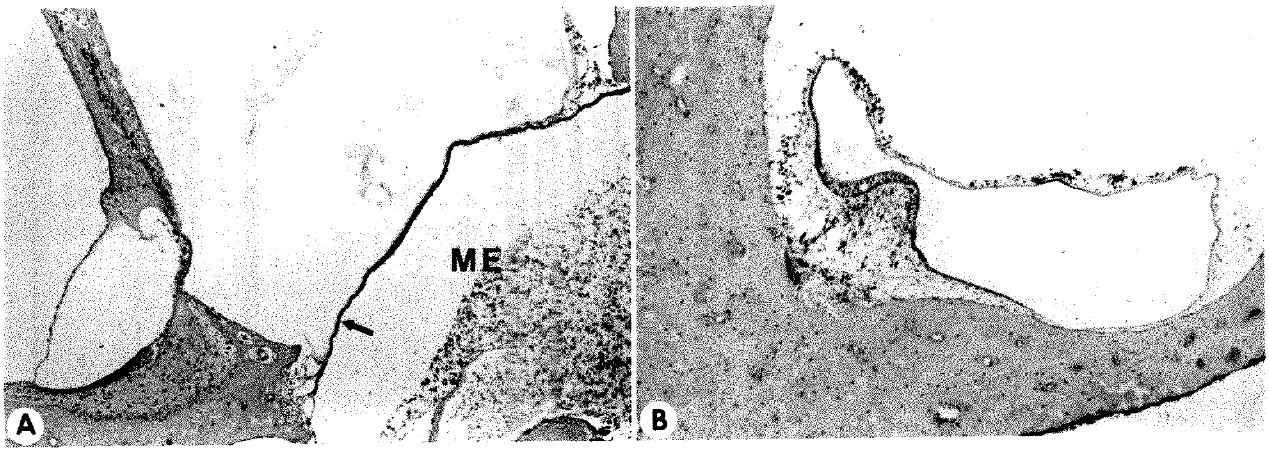

Fig 7. Aural barotrauma from right ear of animal 11 in Table (H & E). A) In middle ear (ME), blood clot is seen. Blood and precipitated material are seen in scala tympani. Arrow — round window membrane. Degeneration of organ of Corti is recognized. B) Hemorrhage in semicircular canal. Blood is seen in perilymph near endolymphatic space, which had slight tendency to collapse. Blood is also recognized near crista ampullaris. Staining does not show obvious degeneration in cells of crista ampullaris.

condition, which is not usually experienced by humans, may have altered the results, it was thought that the middle and inner ear disorders observed in this experiment were based fundamentally on aural barotrauma. It became evident that guinea pigs sustain more aural barotrauma than do human beings. Their susceptibility may be related to the patency of the cochlear aqueduct. We consider that the wider the cochlear aqueduct, the easier the displacement of the round window and basilar membrane.

During the exposure to the pressure change, spontaneous nystagmus occurred toward the contralateral side of the more impaired ear. According to Ewald's law, ampullifugal endolymph flow might have occurred around the crista of the horizontal semicircular canal in the impaired ears. As a rotatory component clearly was observed in the spontaneous nystagmus in two animals, the vertical canals were considered to be influenced. There was a possibility that the change in the composition of inner ear fluid transiently altered the vestibular function. Though we could not find the rupture of Reissner's membrane or the basilar membrane, inner ear hemorrhage and lack of uniformity in staining of inner ear fluid, as shown in Fig 7, suggested the change in the composition of inner ear fluid. There was also a possibility that the increased pressure of the inner ear fluid exerted an influence on the blood flow of the inner ear. Nakashima and Ito[21] stated that cochlear blood flow ceased when the pressure of the inner ear fluid reached the level of intracochlear arterial pressure. It is assumed that the blood flow of the vestibular end-organs also may be influenced by the pressure of the inner ear fluid.

Auditory dysfunction in this experiment showed significant variations, not only among the experimental animals, but also between the right and the left ears. In Preyer's reflex, we could find the difference in size of the movements between the right and the left pinnas in six animals exposed to pressure loading. This asymmetric Preyer's reflex also was observed in guinea pigs in which one external ear canal was plugged.

Both unilateral perceptive and unilateral conductive hearing losses can cause an asymmetric Preyer's reflex in guinea pigs. Gerstner's report[22] described that Stein stated that guinea pigs bereft of one cochlea lost Preyer's reflex of the affected side. It is assumed that Preyer's reflex has a stronger uncrossed reflex arc than a crossed one.

Lamkin et al[23] changed the ME pressure through a cannula inserted into the ME space and produced experimental aural barotrauma in guinea pigs. They observed the inner ear hemorrhage most commonly in the scala tympani of the basal turn close to the round window in a pattern more or less similar to that in our experiment. We considered that at least a part of the inner ear hemorrhage in our experiment originated from blood vessels of the round window membrane. The round window membrane hemorrhage often accompanied the round window membrane rupture.

There was no direct relationship between auditory dysfunction and rupture or hemorrhage of the round window membrane. Weisskopf et al[24] reported the effects of removal of the round window membrane in guinea pigs and found an average decrease in cochlear microphonics of only 6 dB following the procedure. Fukaya and Nomura[25] reported that a simple incision on the round window membrane in guinea pigs caused no remarkable changes in cochlear function after the membrane was closed. The variability of the auditory and vestibular dysfunction in round window membrane rupture may be caused by variations in the lesions inside the inner ear, rather than differences in state and extent of the rupture.

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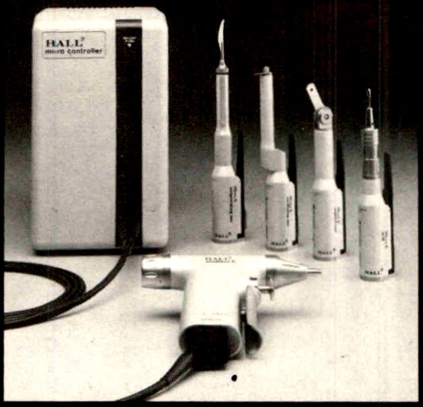

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Animals that had collagen-induced autoimmune inner ear disease were treated with anti-inflammatory drugs: Solu-Medrol (steroid), sulindac (nonsteroid), or a combination of both. Temporal bones from drug-treated animals were examined for histopathologic and immunohistochemical changes, and sera were examined for levels of circulating antibody to type II collagen. Therapy was beneficial to the animals whether the drugs were administered alone or in combination; however, fewer lesions were observed in animals given either drug alone. Further, animals treated with steroid alone showed the least amount of inner ear damage. Immunohistochemical changes and serum levels of antibodies against type II collagen correlated with the pathologic changes. These findings suggest that both steroidal and nonsteroidal anti-inflammatory drugs may have potential therapeutic value in the treatment of autoimmune ear disease.

KEY WORDS — anti-inflammatory drugs, autoimmune ear disease, hearing loss, type II collagen.

INTRODUCTION

The first case report of human autoimmune sensorineural hearing loss was written by McCabe.[1] This entity was established on the basis of its clinical pattern and response to treatment. McCabe observed a dramatic improvement of hearing in patients treated with dexamethasone and cyclophosphamide combination therapy. Further, patients with Cogan's syndrome, another otopathologic disorder thought to be an autoimmune disease, responded favorably when given steroid therapy.[2] No histologic data were reported in these patients, however.

Collagen ear disease in rats is an animal model of autoimmune ear disease that can be produced by an intradermal injection of native type II collagen in complete or incomplete Freund's adjuvant.[3] The disease, which resembles human ear disease in some respects, is not completely understood, but appears to be the result of an autoimmune response to type II collagen.[3,4] Collagen ear disease appears to be one of many collagen-induced diseases such as rheumatoid arthritis, scleroderma, and necrotizing vasculitis.[5,6] Although a diverse family of collagen autoimmune diseases exists, thus far all have been treated with steroidal and nonsteroidal anti-inflammatory drug therapy with some success,[7] except for collagen-induced autoimmune ear disease (CIAED).

This study examined steroidal and nonsteroidal anti-inflammatory drug treatment as well as combination drug therapy for effectiveness in preventing or ameliorating CIAED. The effectiveness of drug therapy was assessed histologically and immunologically in animals with CIAED.

MATERIALS AND METHODS

Animals. Inbred female Lewis rats (Office of Mammalian Genetics and Animal Production Section of the National Cancer Institute, Frederick Cancer Research Center, Frederick, Md) and outbred female Wistar rats (Harlan, Indianapolis, Ind), weighing 140 to 160 g, were used. Rats were housed in groups of three in wire-bottomed metal cages and fed standard laboratory food and water ad libitum.

Preparation of Type II Collagen. Type II collagen was isolated and purified from bovine articular cartilage as previously described.[5] The collagen was confirmed to be pure by amino acid analysis, sodium dodecyl sulfate polyacrylamide gel electrophoresis, and uronic acid analysis.

Drugs Used for Therapy. Sodium succinate ester of methylprednisolone (Solu-Medrol, Elkins-Sinn Inc, Cherry Hill, NJ), a short-acting steroid, was available as an amorphous solid. Sulindac (Clinoril; Merck, Sharp & Dohme, West Point, Pa), a nonsteroidal anti-inflammatory derivative defined chemically as (Z)-5-fluoro-2-methyl-1-[[*p*-(methylsulfinyl) phenyl] methylene]-1*H*-indene-3-acetic acid, was available in tablet form. Sulindac inhibits prostaglandin synthesis by sulfide metabolites.

The drugs were prepared fresh prior to administration. The drugs were suspended in bacteriostatic water and injected intramuscularly (IM). Solu-Medrol was administered at 40 mg/kg per animal, sulindac at 150 mg/kg per animal.

Treatment Protocol. Rats were divided into seven groups (Table 1). Animals were given 200 μg of native bovine type II collagen (BIIn) in complete Freund's adjuvant intradermally in a hind footpad and boosted twice in the base of the tail. The drugs were given IM after the animals were given the BIIn at weekly intervals for a total of three treatments.

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TABLE 1. ANIMAL GROUPS

Group	*Treatment*
A	Control 1, 0.01 *M* acetic acid in CFA
B	Control 2, 0.01 *M* acetic acid in CFA and treated 3 times with Solu-Medrol (40 mg)
C	Control 3, 0.01 *M* acetic acid in CFA and treated 3 times with sulindac (150 mg)
D	Immunized 3 times with BIIn (200 μg in CFA)
E	Immunized 3 times with BIIn (200 μg in CFA) and treated immediately with Solu-Medrol (40 mg)
F	Immunized 3 times with BIIn (200 μg in CFA) and treated immediately with sulindac (150 mg)
G	Immunized 3 times with BIIn (100 μg in CFA) and treated with Solu-Medrol (20 mg) and sulindac (75 mg)

BIIn — native bovine type II collagen, CFA — complete Freund's adjuvant.

Animals from each group were killed 2 weeks after the last treatment. Control rats received 0.01 mol/L acetic acid in complete Freund's adjuvant.

Histopathology and Immunofluorescence. For histopathologic studies, the right sides of the temporal bones were dissected en bloc, fixed in 10% neutral buffered formalin, decalcified with 5% trichloroacetic acid, embedded in celloidin and paraffin, cut 7 μm horizontally, and stained with hematoxylin and eosin. Histopathology was graded according to whether there was no degeneration, mild degeneration, or severe degeneration.

For immunofluorescence studies, the left sides of the temporal bones were fixed in 95% ethanol, decalcified with 5% EDTA (pH 7.4), embedded in paraffin before sectioning, and treated with fluorescein isothiocyanate (FITC)–conjugated goat anti-rat IgG or C3.

Serologic Analysis. Antibodies to type II collagen were measured by a solid-phase enzyme-linked immunosorbent assay (ELISA). Briefly, microtiter plates were coated with 5 μg/mL of BIIn overnight. The plates were washed three times with PBS with 0.5% Tween. Serum samples were diluted in Jerry Gross buffer with 0.5% Tween and incubated for 2 hours at room temperature. The wells were washed three times and incubated with peroxidase-conjugated goat anti-rat IgG. The wells then were washed and treated with O-phenylenediamine. The absorbance was read at 490 nm in a Dynatech MR 580 micro-ELISA autoreader.

Statistical Analysis. Statistical analyses were determined using Fisher's direct probability method.

RESULTS

HISTOPATHOLOGIC STUDY

Sensory Degeneration. Mild degeneration of the organ of Corti, characterized by slightly atrophied outer hair cells, inner hair cells, pillar cells, Deiters' cells, Claudius' cells, and Hensen's cells, and slightly swollen inner sulcus cells, was observed in five of the nine immunized rats. Slightly swollen inner sulcus cells and Claudius' cells were observed in 38%, 44%, and 66% of rats treated with BIIn and steroid, BIIn and sulindac, and BIIn and a combination of both steroid and sulindac, respectively (Table 2).

All four of the immunized Lewis rats and two of the five Wistar rats immunized with BIIn (Fig 1B) had spiral ganglion cell degeneration that was characterized by swollen cell bodies, clear cytoplasm, and pyknotic nuclei. The degeneration was more severe in the upper turn than in the lower turn; however, the degeneration of spiral ganglia in which 50% of cell bodies were swollen was observed in only one fourth of the rats immunized with BIIn and treated with steroid (Fig 1C).

TABLE 2. HISTOPATHOLOGIC FINDINGS

	Degeneration of Organ of Corti			*Degeneration of Spiral Ganglia*			*Degeneration of Macula Sacculi*			*Degeneration of Crista Ampullaris*			*Vascular Changes in Cochlea*		
Group	−	+	++	−	+	++	−	+	++	−	+	++	−	+	++
Lewis rats															
Control (4)	4	0	0	4	0	0	4	0	0	4	0	0	3	1	0
Control + St (7)	6	1	0	6	1	0	7	0	0	6	1	0	5	2	0
Control + Su (4)	4	0	0	4	0	0	4	0	0	4	0	0	4	0	0
BIIn (4)	1	2	1	0	3	1	1	3	0	1	2	1	0	3	1
BIIn + St (8)	5	3	0	6	2	0	7	1	0	6	2	0	5	3	0
BIIn + Su (4)	2	2	0	2	2	0	3	1	0	3	1	0	2	2	0
BIIn + St + Su (4)	1	3	0	1	3	0	1	3	0	2	2	0	1	3	0
Wistar rats															
Control (3)	3	0	0	3	0	0	3	0	0	3	0	0	3	0	0
Control + St (5)	5	0	0	5	0	0	5	0	0	5	0	0	5	0	0
Control + Su (5)	5	0	0	5	0	0	5	0	0	5	0	0	4	1	0
BIIn (5)	2	3	0	3	2	0	2	3	0	3	2	0	0	4	1
BIIn + St (5)	3	2	0	4	1	0	4	1	0	4	1	0	2	3	0
BIIn + Su (5)	3	2	0	4	1	0	4	1	0	3	2	0	2	3	0
BIIn + St + Su (5)	2	3	0	4	1	0	3	2	0	3	2	0	2	3	0

Severity of lesions graded from − (no degeneration) to ++ (severe degeneration). Numbers in parentheses represent number of animals in each group. Animals were divided into seven groups (Table 1). Control + St indicates animals treated with drug alone. BIIn + St indicates animals immunized with bovine type II collagen and treated with steroid (Solu-Medrol).

St — steroid (Solu-Medrol), Su — sulindac, BIIn — native bovine type II collagen.

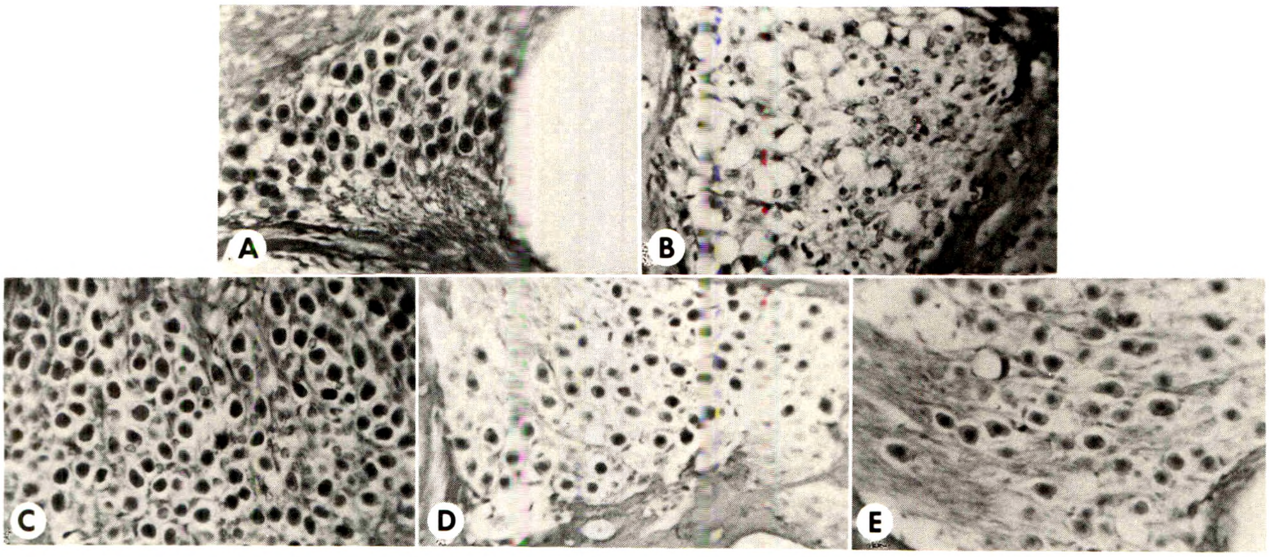

Fig 1. Cochlear neurons of Lewis rats (H & E, original x240). A) Normal population and appearance from control rat. B) Severe vacuolar degeneration from rat immunized with native bovine type II collagen (BIIn). Cell bodies are greatly swollen, cytoplasm is clear, and nuclei are pyknotic. C) Neurons of rat immunized with BIIn and treated with steroid show that about 50% of cell bodies are slightly swollen. D) Neurons from rat immunized with BIIn and treated with sulindac show that more than 70% of cell bodies are slightly swollen. E) Cochlear neurons from rat immunized with BIIn and treated with steroid and sulindac show that more than 70% of cell bodies are swollen, cytoplasm of some neurons is clear, and nuclei are pyknotic.

Three of the nine immunized rats treated with sulindac and four of the nine immunized rats treated with steroid and sulindac showed degeneration of spiral ganglia (Fig 1D,E and Table 2).

Mild vacuolar degeneration of sensory cells, characterized by swelling and clear cytoplasm, also was observed in the macula sacculi in the immunized animal groups; however, the percentage of animals that developed this degeneration was appreciably lower in immunized animals treated with either steroid or sulindac (Table 2).

Vacuolar degeneration also was observed in the sensory cells of the crista ampullaris from five of nine rats; however, the immunized animals with drug treatment had a lower incidence of sensory cell degeneration (ten of 31; Tables 2 and 3).

The utricles of all animals were normal (data not shown). Statistical analysis of the data indicated that steroid therapy was effective in slowing sensory degeneration observed in the rats immunized with BIIn ($p<.001$, Table 3). The other treatment protocols showed no statistically significant amelioration of sensory degeneration.

Disorders in Cochlear Blood Vessels. Slight fibrotic changes in the perivascular area of the cochlear blood vessels were observed in a small number of control rats (Fig 2A). Slight to moderate fibrotic changes in the same area were observed in seven of nine immunized rats and six of seven immunized rats given combination drug therapy, whereas half of the immunized rats treated with either steroid (six of 13) or sulindac (five of nine) developed fibrotic changes (Fig 2C,D). In addition to the fibrotic changes observed in the perivascular area, thickening of the vessel walls was observed in two of the immunized rats (Fig 2B and Table 2).

The vascular changes noted in the cochlear vessels of rats immunized with native type II collagen was significant ($p<.001$) compared to those of the control animals (Table 4). Steroid therapy was significantly effective in improving the vascular changes observed in the cochlear vessels of immunized rats ($p<.01$), as was sulindac therapy ($p<.05$; Table 4). Though drug therapy reduced the degree of lesion, it did not completely prevent the damage from occurring.

IMMUNOHISTOLOGIC STUDY

Immunofluorescence studies were performed to determine the site and extent of IgG and C3 deposits in this CIAED model. The majority of the rats immunized with BIIn had extensive IgG deposits in the perivascular area of the cochlear blood vessels. Fewer IgG deposits were observed in the perivascular area of the cochlear blood vessels from immunized animals treated with drugs (groups E

TABLE 3. EFFECT OF DRUG TREATMENT ON DEVELOPMENT OF SENSORY DEGENERATION IN COLLAGEN TYPE II - IMMUNIZED RATS

Group	*Degeneration of Organ of Corti* −	+	*% Occurrence of Degeneration*
Control (28)	27	1	4
BIIn (9)	3	6	67
BIIn + St (13)	8	5	39
BIIn + Su (9)	5	4	44
BIIn + St + Su (9)	3	6	67

Numbers in parentheses represent number of animals in each group.

BIIn — native bovine type II collagen, St — steroid (Solu-Medrol), Su — sulindac.

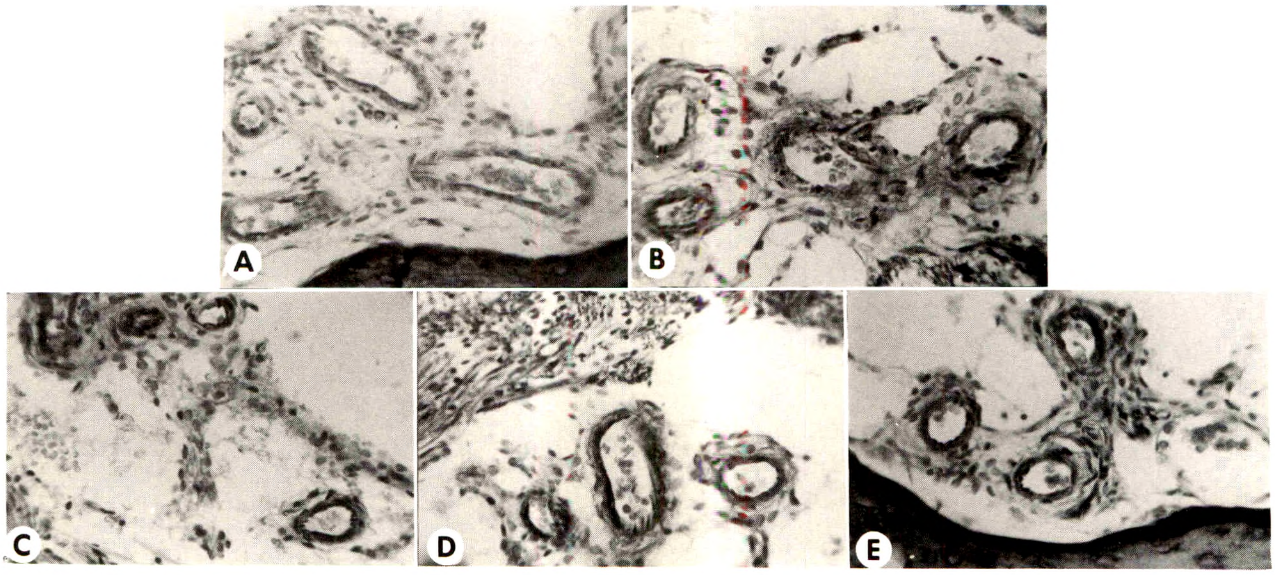

Fig 2. Cochlear blood vessels of Lewis rats (H & E, original x240). A) Perivascular area of control rat showing slight fibrotic changes. B) Perivascular area from rat immunized with native bovine type II collagen (BIIn), with thickening of vessel walls and severe fibrotic changes. C) Slight fibrotic change in perivascular area of rat immunized with BIIn and treated with steroid. D) Slight fibrotic change in perivascular area of rat immunized with BIIn and treated with sulindac. E) Moderate fibrotic change in perivascular area of rat immunized with BIIn and treated with steroid and sulindac.

through G; Table 1 and Fig 3). Similar results were obtained for anti-rat C3.

ANTIBODY TITER TO TYPE II COLLAGEN

The measurements of the antibody titer to type II collagen were consistent with the severity of histopathologic changes. The more severe the lesions, the higher the antibody titer to type II collagen. In nonimmunized animals the results were negative for detectable antibody against BIIn. Serum antibody levels of type II collagen were measured after the animals were killed. Immunized animals that received no treatment showed high antibody levels, whereas less antibody response was measured in steroid-treated, immunized animals (Table 5).

DISCUSSION

Since McCabe reported a case of human autoimmune sensorineural hearing loss, several clinicians have pointed out the usefulness of steroids in the management of this disorder.[8-10] Furthermore, nonsteroidal anti-inflammatory drugs have been shown to be useful in the management of a variety of autoimmune diseases.[7] This study demonstrates the effectiveness of both steroidal and nonsteroidal anti-inflammatory drugs in the management of CIAED in rats. Histopathologic and immunologic results clearly support a marked reduction in severity of the inner ear lesions concomitant with a reduction in the deposition of IgG and C3 in the damaged areas.

In general, the inner ear lesions produced by immunization with type II collagen were more severe in the inbred Lewis rat than in the outbred Wistar rat, and this result supports earlier observations of Yoo et al.[6]

Methylprednisolone (a short-acting steroid) is an anti-inflammatory and immunosuppressive agent. Its effects on inflammatory and immune phenomena include inhibiting leukocyte movement, leukocyte function, and humoral factors. The most important anti-inflammatory effect of steroid administration is its ability to inhibit the recruitment of neutrophils, monocytes, and macrophages to an inflammatory site.[7] Steroids do not suppress the production of lymphokines by lymphocytes, but rather, they inhibit the ability of these soluble mediators to recruit cells necessary for the expression of cellular immunity, and they are potent inhibitors of prostaglandin (PG) synthesis by inhibiting arachidonic acid release from phospholipids.[11-13]

Nonsteroidal anti-inflammatory agents also inhibit PG synthesis by inhibiting the cyclo-oxygenase enzyme that converts arachidonic acid to the cyclic endoperoxide.[7]

It is well known that tissue injuries enhance the immune response. This study determined whether steroidal or nonsteroidal anti-inflammatory drugs

TABLE 4. EFFECT OF DRUG TREATMENT ON DEVELOPMENT OF VASCULAR CHANGES IN COCHLEA OF TYPE II COLLAGEN - IMMUNIZED RATS

Group	*Vascular Changes* –	+	*% Occurrence Changes in Cochlea*
Control (28)	24	4	14
BIIn (9)	0	9	100
BIIn + St (13)	7	6	46
BIIn + Su (9)	4	5	56
BIIn + St + Su (9)	3	6	67

Numbers in parentheses represent number of animals in each group.

BIIn — native bovine type II collagen, St — steroid (Solu-Medrol), Su — sulindac.

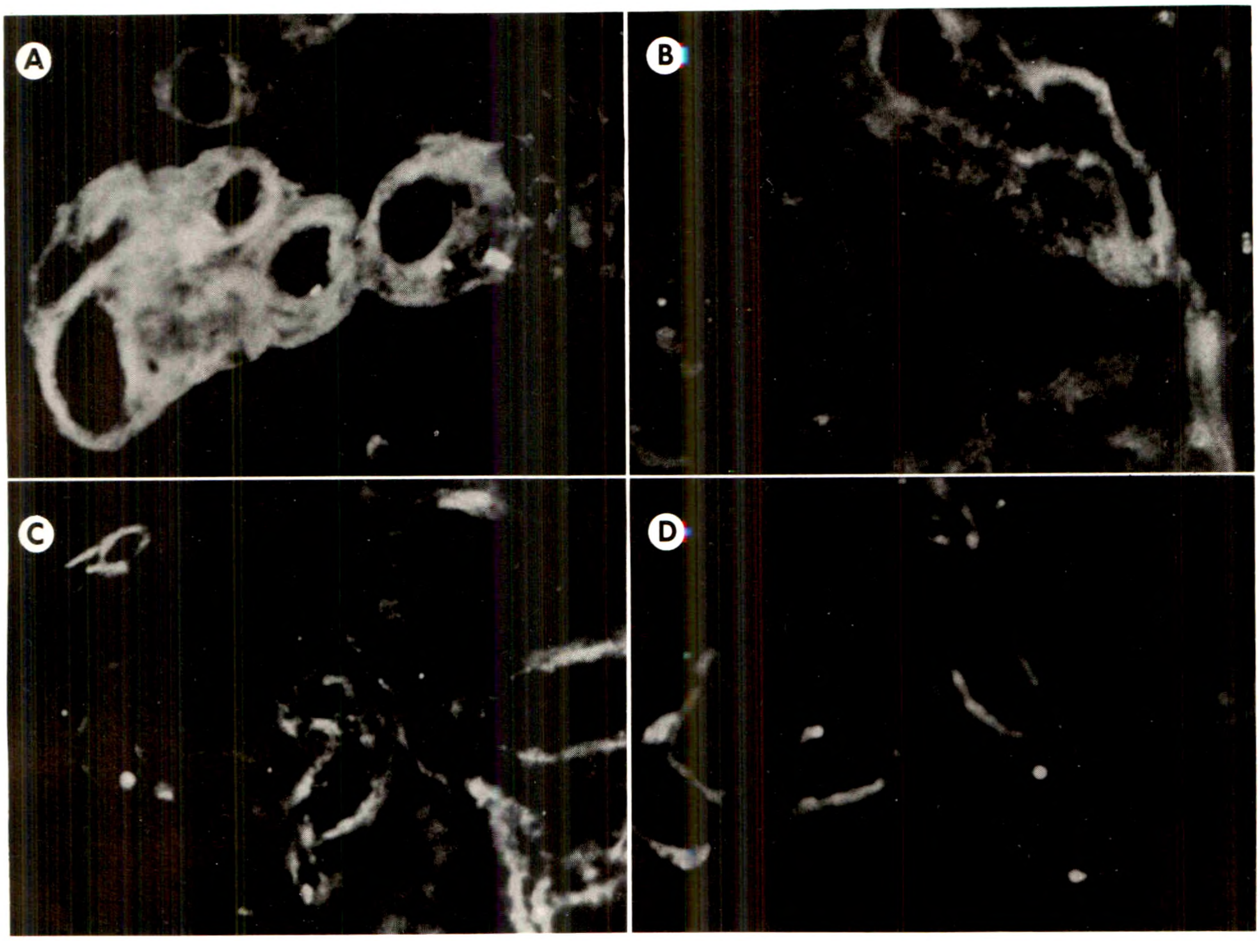

Fig 3. Immunofluorescence micrograph with anti-rat IgG in cochlear blood vessels of Lewis rats (FITC-labeled antibodies, original x180). A) Strong IgG deposition in perivascular area from rat immunized with native bovine type II collagen (BIIn). B) Cochlear blood vessel from rat immunized with BIIn and treated with steroid and sulindac shows less IgG deposition than in A. C) Cochlear blood vessel from rat immunized with BIIn and treated with sulindac shows less IgG deposition than in B. D) Cochlear blood vessel from rat treated with BIIn and steroid shows weak IgG deposition in perivascular area.

alone would be ototoxic. Our data indicated that these drugs were not ototoxic agents at the doses and duration studied. It is obvious that the half-life, potency, and duration of action of the anti-inflammatory drugs depend on the dose and route of administration. Clinicians[1,8-10] routinely prescribe oral administration of dexamethasone (a slower-acting glucocorticoid) in the treatment of patients with autoimmune sensorineural hearing loss. Since it is difficult to give drugs orally to rats, however, IM injections were substituted. This route of drug administration might release the drug slowly and exert an effect for a more prolonged period than the intravenous injection or oral administration of the drug. Whether the route of drug administration is important remains to be studied.

The present data indicate that the dose of steroidal or nonsteroidal anti-inflammatory drugs used in this study was effective in reducing the inner ear lesions of CIAED observed in the animals. The combination of both drugs appears to be less effective than either drug alone in the treatment of CIAED. Statistically, combination therapy was not correlated with a significant difference in the number of lesions; however, there was a tendency for the lesions to be less severe in the organ of Corti. The reason that combination therapy was not as effective is not clear. It is possible that the effective range of the drug doses given was too high in combination. More studies are necessary to determine if combina-

TABLE 5. ANTIBODY TITER TO TYPE II COLLAGEN MEASURED BY ELISA

	Antibody (Mean Absorbance at 490 nm)	
Group	*Lewis Rats*	*Wistar Rats*
Control	0.005	0.010
Control + St	0.002	0.012
Control + Su	0.001	0.008
BIIn	0.989	1.450
BIIn + St	0.636	0.525
BIIn + Su	0.938	1.010
BIIn + St + Su	0.761	1.247

A 1:100 dilution of serum was used. Animals were divided into seven groups (Table 1). Control + St indicates animals treated with drug alone. BIIn + St indicates animals immunized with bovine type II collagen and treated with steroid (Solu-Medrol).

St — steroid (Solu-Medrol), Su — sulindac, BIIn — native bovine type II collagen.

tion therapy at lower doses would be useful in the treatment of CIAED.

The vascular disorder in the cochlea is thought to have an important role in the pathogenesis of autoimmune ear diseases.[1,14] Other lesions that develop are thought to derive from hypoxia or anoxia due to vascular damage in the cochlea. The drugs used in this study were more effective in reducing the vascular changes than in reducing sensory degeneration. We speculate that these drugs might play an important role in reducing the primary immunologic injury but do not have much influence on the secondary injury. High antibody titers detected in the immune sera and the presence of immunoglobulin and complement in the damaged tissue suggest that cytotoxic or immune complex immunologic injuries were involved, alone or in combination.

The lower titer and the smaller IgG and C3 deposition in groups E through G (Table 1) also indicated that steroidal or nonsteroidal anti-inflammatory agents are effective immunologically. These drugs may act to block the helper T cell function or have a direct effect on B-lymphocytes.

Prostaglandins are thought to play a crucial role in the regulation of the fluid dynamics of the inner ear. The local and general concentrations of PG should be assayed and compared to the dose and time of administration of these kinds of drugs to determine if their levels are altered. Jung and Juhn[15] have measured levels of PGE2 and 6-keto-PGF1α in the perilymph of normal and PG-inhibitor–treated chinchillas. They found that the levels of both PGE2 and 6-keto-PGF1α, which are high in normal perilymph, decreased dramatically after treatment with indomethacin or aspirin and concluded that the high concentration of PGs in the normal perilymph suggests an active role of PGs in the normal function of the inner ear. Our preliminary results showed that PG is elevated in the perilymph of this animal model.[16] The level of PG in the perilymph needs to be explored further for us to better understand the role of PG in CIAED.

The present study suggests that our animal model of CIAED might be useful in studying the effect of new drug therapy in this disease. Further studies are necessary to analyze the usefulness of steroidal and nonsteroidal anti-inflammatory drugs in human autoimmune sensorineural hearing loss.

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EFFECTS OF STRIPPING AND LASER EXCISION ON VOCAL FOLD MUCOSA IN CATS

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We compared the effects of stripping and laser excision on vocal fold mucosa in cats. Of particular interest were the comparative effects of each procedure on the mucosa's sensory structures. Mucosa was stripped from one vocal fold in three cats, lased in three additional cats, and histologically examined at 1-, 2-, and 3-week intervals postoperatively. Results indicate that both procedures produce unique and degenerative effects that are still apparent 3 weeks after operation; however, nervous elements in lased tissue samples appeared less disrupted than in stripped tissue. Unique effects on the composition of epithelial tissue also were noted for the two procedures. Implications for voice quality in human patients undergoing similar procedures are discussed.

KEY WORDS — vocal fold laser excision, vocal fold stripping.

Some speakers who undergo an operation for removal of lesions related to vocal abuse, ie, vocal nodules, may not experience an immediate or predictable recovery. Rather, following the operation and a specified period of voice rest, the patient may resume talking, only to discover that the voice quality is unchanged, or even worse, as compared to the preoperative voice. This may be true in spite of evidence from an indirect laryngeal examination that the vocal cords appear normal in structure and function. In our experience, such an outcome can result from only one operation; with repeated operations, it almost is assured. In a previous study, we[1] reported that repeated strippings of the vocal fold mucosa in cats were accompanied by increased fibrous tissue in the regenerated mucosa and by decrements in mucosal sensory receptors known to mediate airflows and air pressures in the airway. Assuming a similar response in humans, changes in the mucosa's epithelial or nervous structures might be related realistically to alterations in voice quality that persist following an operation, perhaps even after the larynx, by clinical measures, has been pronounced normal. We suggested that a better alternative for treating vocal nodules is voice therapy and that should this fail, carbon dioxide laser excision of the lesion may represent a better choice than stripping. While the laser is destructive to tissues, it would seem to involve a smaller area of mucosa than that affected by operative stripping.

A number of studies have compared the effects of laser incision and scalpel incision on epithelial tissues and subsequent wound healing.[2-5] In general, these investigations suggest that the relative benefits of CO_2 laser incisions include minimal damage to adjacent tissues, a decreased inflammatory response, and less contraction of tissue in the wound site. The regeneration of epithelial tissue, however, appears to be somewhat delayed in CO_2 laser incisions as compared to scalpel incisions, perhaps because of eschar that forms on the wound margins of thermal necrosis, delaying the initiation of epithelialization, though apparently not the rate of re-epithelialization.[2,3] Hall et al[2] reported that scalpel wounds in skin had re-epithelialized in 2 days, whereas wounds of the same size induced by CO_2 laser required 7 or 8 days to re-epithelialize. Beyond re-epithelialization, Fisher et al[5] reported that laser incisions of the buccal mucosa in dogs demonstrated no evidence of damage after 28 days, while scalpel incisions of the same size produced an area of contracted scarring that was still visible at 48 days.

Ben-Bassat et al[6] have demonstrated that epithelial tissue may be more vulnerable to the effects of CO_2 laser than some other tissues, including desmosomes, cell nuclei, collagen, and erythrocytes. These authors reported that, while lased epithelial tissue showed effects of necrosis to a distance of 250 µm from the affected edge, effects noted for other tissue types did not extend beyond 30 to 50 µm from the wound site. One question, however, that has been raised about the laser is the possibility, seemingly remote, that ejected tissue may retain its functional viability and travel to distant sites.

The current study was undertaken in an attempt to compare the effects of CO_2 laser excision and operative stripping on vocal fold mucosa in cats. Of particular interest was whether the laser would produce changes in the composition of the epithelium and its sensory network similar to those previously observed with vocal fold stripping. The mechanism of tissue incision with the CO_2 laser is the vaporization of tissue water; that is, in response to the laser,

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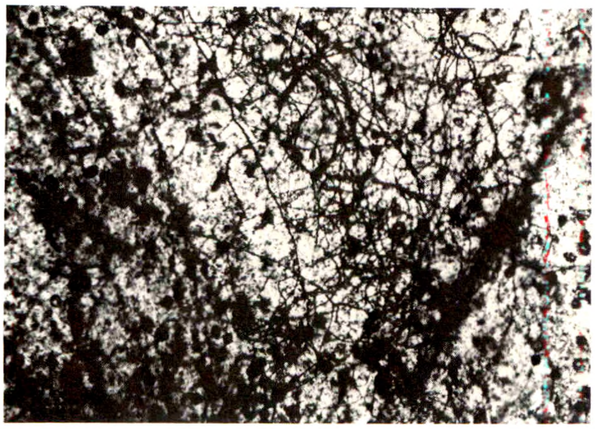

Fig 1. Dense population of cell bodies and nerve fibers in normal mucosa (original x250).

water in cells increases in temperature to the boiling point. The rapid expansion produced by the vaporization process causes cell disruption in which solid cellular material is ejected.[2] How such thermal trauma to tissues compares with the trauma induced by stripping, and how this may be reflected at certain stages in the re-epithelialization process, is unclear.

METHODS

Six cats, similar in size and housed in the same laboratory environment, were used. Three cats were selected to have the vocal fold mucosa stripped from the left vocal fold, and the remaining three cats were to undergo laser excision of the left fold.

Prior to operation, the cats were anesthetized by a veterinary anesthesiologist with intramuscular acepromazine maleate (0.1 mg/kg) followed by induction with intravenous thiamylal sodium (5 to 10 mg/kg). Following anesthesia, an otolaryngologist examined the condition of each cat's larynx under direct laryngoscopy. When the larynx had been judged normal, mucosa from each cat's left vocal fold was either stripped or lased. Both procedures were performed under a Zeiss operating microscope in a manner as analogous as possible to the procedures typically performed in humans. Stripped tissues were removed in an anterior-posterior direction, with extreme care taken to remove only mucosa. One departure from the normal operative routine for human subjects was the amount of tissue lased. For the sake of uniformity, the surgeon attempted to lase tissue from the same anterior-posterior extent along the medial fold as was involved in the stripping procedures. In a typical laser excision, only mucosa immediately below and around the nodule would be affected by the laser. Intensity of the CO_2 laser beam (Kelly-Coherent) was set at 20 W, with a duration of 50 ms. After completion of the six operations, the cats were observed until recovery from anesthesia was judged complete, then returned to their quarters.

Seven days postoperatively, one cat each from the lased and stripped groups was killed and the larynx removed. The left vocal fold of each cat was divided into four quadrants from an anterior-posterior line extending along the medial edge of the fold and a superior-inferior line at the midpoint of the membranous fold. The untouched right vocal fold was sectioned in the same manner. In each cat, mucosa from this fold served as control tissue. Then mucosa from the right and left folds was removed and prepared for microscopic examination according to a modification of a gold chloride stain described by Adzaku and Wyke[7] and previously detailed by Leonard et al.[1] This process was repeated with two additional cats at 2 weeks postoperatively and with the remaining lased and stripped cats at 3 weeks postoperatively.

RESULTS

Examples of nervous tissue in normal mucosa pre-

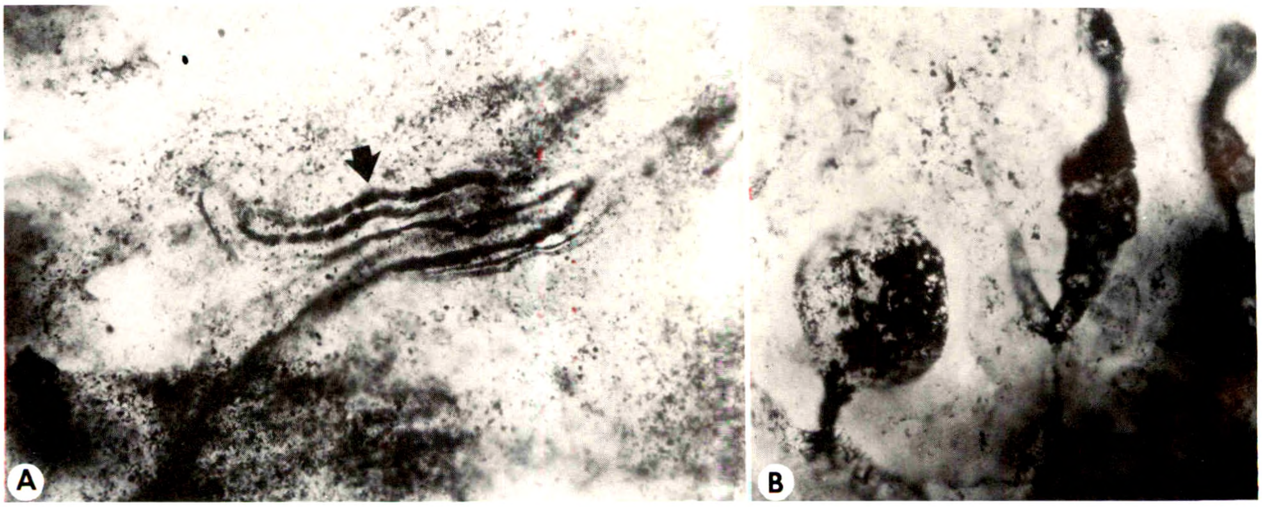

Fig 2. Two weeks after stripping or laser excision. A) Stripped mucosa's nervous tissue (arrow) is segmented, suggesting degenerative process (original x485). B) In lased tissue, cell body is engorged and appears to be undergoing degeneration (original x1,000).

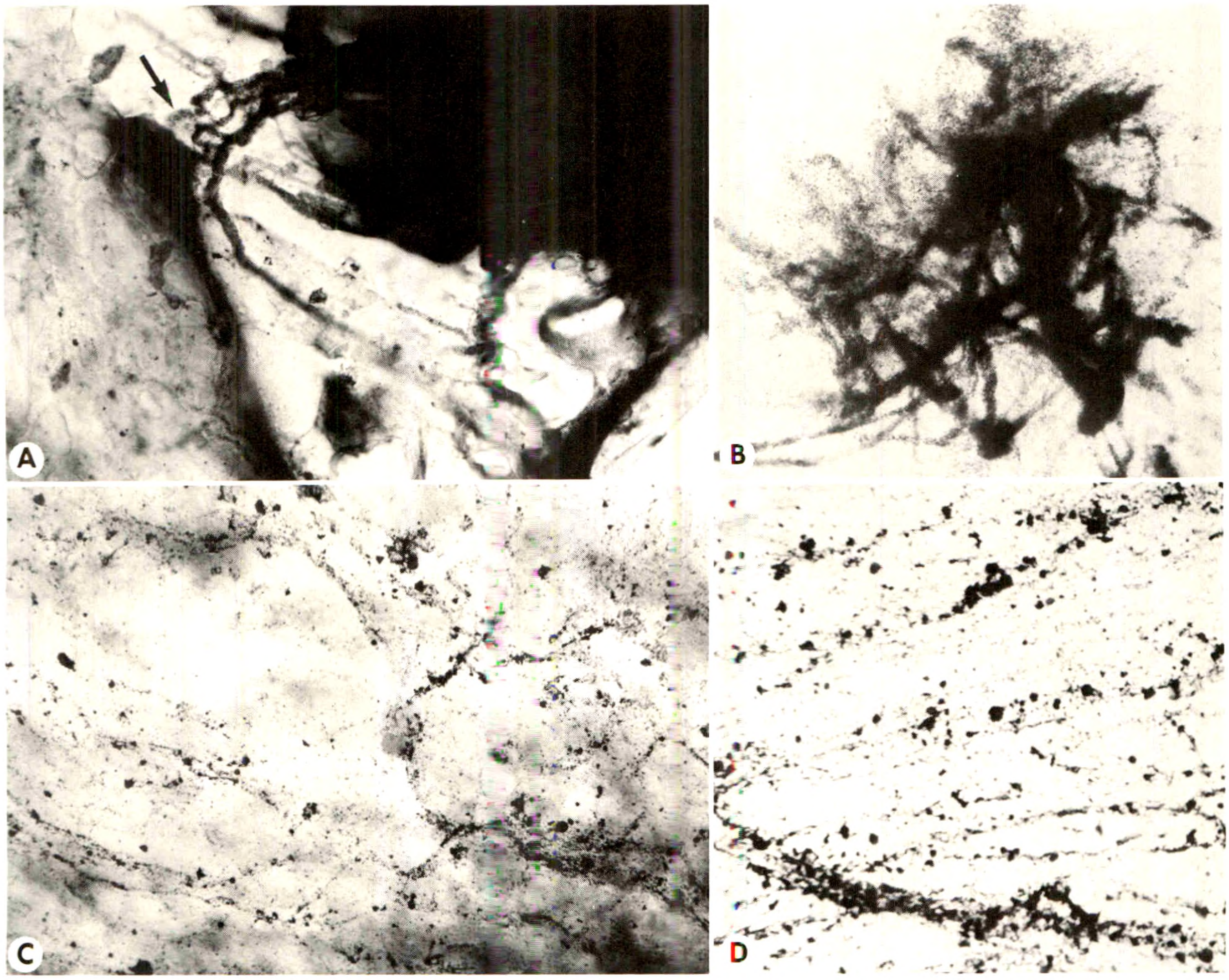

Fig 3. Three weeks after stripping or laser excision. A) Stripped mucosa's nervous tissue (arrow) appears curled (original x375). B) Lased tissue with neuritic tangle (original x100). C) Residue of nervous tissue in stripped mucosa (original x250). D) Lased mucosa retains striated appearance suggestive of underlying neural substrate (original x250).

viously were described in some detail[1] and are reviewed here only briefly. A dense population of normal sensory receptors in association with nerve fibers, presented in Fig 1, is typical of tissue samples observed. Two types of sensory receptors described by Adzaku and Wyke[7] also were characteristic of the samples examined. These include a medium sized (100 x 80 μm), thickly encapsulated corpuscle innervated from a myelinated afferent fiber, and a second, smaller globular corpuscle (20 x 10 μm), less frequent than the first type, innervated by fine myelinated afferent fibers (4 to 5 mm in diameter).

Tissue removed from the stripped fold 2 weeks postoperatively is illustrated in Fig 2A. While disc-shaped receptors were numerous in these samples, their numbers appeared reduced as compared to those in control tissue. It is apparent from the segmented appearance of the nervous tissue in Fig 2A that it is undergoing alteration. This finding was typical of all stripped tissue examined at this interval and is believed to represent a degenerative process. An example of lased tissue 2 weeks postoperatively is presented in Fig 2B. The engorged, ballooning appearance of the cell body and fiber is interpreted as further evidence of nervous tissue undergoing degeneration. While these enlarged cells were found frequently in lased tissue, however, no examples were noted for stripped tissue at any postoperative interval. It seems possible that the engorgement may be associated with the rapid expansion and increase in volume of cellular fluids exposed to the laser.

An additional example of possible nerve cell degeneration is presented in Fig 3A, representing stripped tissue at 3 weeks postoperatively. The arrow in this Figure is pointing to fibers that appear somewhat curled and contorted. In Fig 3B, an example of lased tissue at 3 weeks postoperatively, a tangled mass of nervous tissue referred to as a neuritic tangle is apparent. This phenomenon typically is associated with regenerative processes in which collagen deposits inhibit new neuritic growth.

Evidence of degeneration of the mucosa's nervous structures was typical of both stripped and lased tis-

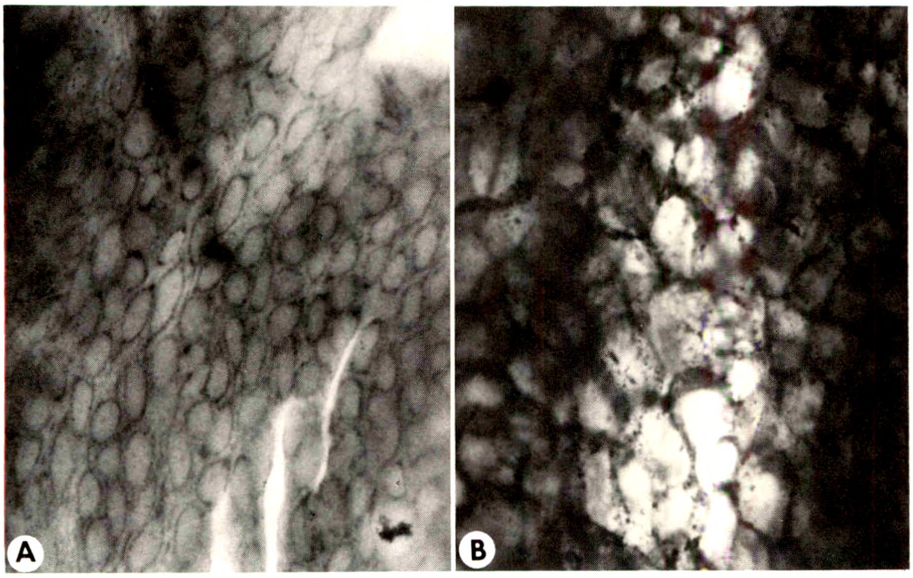

Fig 4. Epithelial tissue 3 weeks after procedures (original x1,000). A) After stripping, some irregularity and large intercellular spaces are revealed. B) After laser excision, highly irregular tissue with some overlapping cells is shown.

sues at 1, 2, and 3 weeks postoperatively. A marked difference between stripped and lased tissues should be noted, however. Presented in Fig 3C is a field of stripped tissue in which some residue of nervous material can be seen in the form of disc-shaped black structures. Presented in Fig 3D is a similar field of lased tissue at 3 weeks postoperatively. The faint, dark, striated lines visible in Fig 3D seem to denote an underlying neural substrate that is more intact than that seen in the stripped tissue. This feature was characteristic of all lased tissues examined.

To date, attempts to quantify nervous structures identified for each procedure at 1, 2, and 3 weeks postoperatively have not revealed clear differences between procedures or across the three postoperative intervals. We are optimistic, however, that results of additional staining techniques currently in progress will enable these kinds of comparisons. Such information might be expected to substantiate further our observation that laser excision is less disruptive to the mucosal nervous network than is vocal fold stripping.

A third feature of both stripped and lased tissues examined in this study was an increase in the fibrous component of the mucosa as compared to that in control tissue. Figure 4A shows epithelial tissue from a stripped fold at 3 weeks postoperatively. In Fig 4B is epithelial tissue from lased mucosa, also at 3 weeks postoperatively. It should be noted that neither of these samples is characteristic of normal vocal fold mucosa; however, the lased tissue is especially aberrant. Epithelial cells in Fig 4B are larger and more irregular in shape than normal epithelial cells, whereas those in Fig 4A are somewhat irregular and demonstrate larger intercellular spaces than normal epithelial tissue. While implications of these differences are not clear, it does seem significant that regenerated epithelial tissue from both procedures was not normal even at 3 weeks postoperatively. We believe that both samples are indicative of an increased fibrous component in the mucosa.

Though not addressing the issue of laser versus stripping per se, Forrester[8] reported that the strength of tissues wounded in a variety of ways, including by knife, typically is reduced from normal for a long period of time. Forrester suggests that even tissues that look well healed may be weak in terms of their tensile strength and pliability. In wound tissue, the strength of repair apparently is related to the formation of scar collagen, which is typically irregular and causes repaired tissue to be weak and brittle. Thus, changes noted in the composition of epithelial tissue for both stripped and lased mucosa are perhaps not surprising.

SUMMARY

In summary, changes observed in the laryngeal mucosa from vocal fold stripping and laser excision procedures include the following.

Nervous structures in both stripped and lased tissues appeared to undergo changes typically associated with the degeneration of nerve cells. These changes were apparent in both sets of tissue at 1, 2, and 3 weeks after operation.

Although nervous tissue was observed to be altered as a result of both stripping and laser excision, two differences were noted. First, some nervous tissue from lased mucosa was enlarged, almost ballooning in appearance. This finding was not noted for stripped tissues and was believed to be related to the thermal effects of the laser procedure. Second, it is our impression that the underlying neural substrate of lased mucosa was more intact and less disrupted than that of stripped mucosa.

Finally, the epithelial ground substance of both stripped and lased mucosa was altered even at 3 weeks postoperatively. Though the alterations were different in stripped and lased tissues, both are believed to reflect an increased component of fibrous granular tissue in the mucosa.

Findings described here represent our best judgment about the effects of two operative procedures on vocal fold mucosa. Artifacts resulting from our manipulation and processing of the tissues cannot be ruled out completely; however, results of the study would seem to warrant at least a few tentative conclusions and speculations.

First, it seems clear that vocal fold mucosa that is regenerated following either vocal fold stripping or laser excision may not be normal tissue, but rather may be altered in terms of both epithelial and neural elements. This finding was true even at 3 weeks postoperatively, when we might expect that the healing process, at least for epithelial tissue, should be complete. Whether or not such tissue changes observed in cats are implicated in the speaker described earlier who experiences a delayed or incomplete recovery from nodule removal remains speculative; however, evidence presented here, consistent with our earlier report,[1] would seem to support the value of a conservative voice therapy approach in the treatment of vocal nodules, one that particularly emphasizes the education of a patient regarding the possible long-term effects of voice abuse and lesions requiring operative excision.

Second, data from this study tentatively appear to support laser excision, as opposed to vocal fold stripping, in the event of a nodule that is not amenable to voice rest or therapy. The consistent finding of neural substrate that was more intact in lased tissues than in stripped tissues, as well as the clinical observation that laser excision of a nodule generally affects a smaller amount of the vocal fold, persuades us that, although destructive, the CO_2 laser may be more benign in this case than traditional fold stripping. On the other hand, the exceptionally deviant epithelial tissue observed following laser excision warrants both further investigation and careful consideration when more extensive excisions, involving more mucosa, may be required.

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INTERNATIONAL WORKSHOP ON CRANIO-FACIAL TRAUMA

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ACOUSTIC ANALYSIS OF VOICES OF PATIENTS WITH NEUROLOGIC DISEASE: RATIONALE AND PRELIMINARY DATA

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This paper presents a rationale for acoustic analysis of voices of neurologically diseased patients, and reports preliminary data from patients with myotonic dystrophy, Huntington's disease, Parkinson's disease, and amyotrophic lateral sclerosis, as well as from individuals at risk for Huntington's disease. Noninvasive acoustic analysis may be of clinical value to the otolaryngologist, neurologist, and speech pathologist for early and differential diagnosis and for documenting disease progression in these various neurologic disorders.

KEY WORDS — acoustic analysis, amyotrophic lateral sclerosis, Huntington's disease, myotonic muscular dystrophy, neurologic disease, Parkinson's disease, phonation, voice.

INTRODUCTION

Voice analysis of neurologically impaired patients may be an important tool in early detection, differential diagnosis, and monitoring of disease progression. Although the perceptual skills of the voice pathologist frequently contribute to these goals,[1-3] recently developed acoustic and physiologic analyses may provide more sensitive and quantitative data on phonatory functioning.[4-6]

Recently, researchers have applied acoustic and physiologic analyses to phonation of patients with neurologic diseases.[6-10] These studies support the notion that acoustic and physiologic analyses may provide quantified phonatory characteristics relative to the location of neurologic injury, which would be of relevant clinical as well as academic value to the fields of voice pathology, otolaryngology, and neurology.

The data presented here are from studies designed to address whether acoustic analysis of voice can 1) contribute to the diagnosis of diseases of different neural subsystems, 2) document progressive degeneration in neurologic diseases, and 3) identify subclinical manifestations of neurologic disease.

Diagnosis of Diseases of Different Neural Subsystems. Myotonic dystrophy, Huntington's disease (HD), and Parkinson's disease are widely differing neurologic diseases that have as one manifestation distinct dysarthrias and disordered phonation.[1,2] In myotonic dystrophy, an autosomal dominantly inherited lower motor neuron disease, flaccid dysarthria[1] and "weak and monotonous" phonation occur.[11] In HD, a dominantly inherited disorder characterized by degeneration of basal ganglia and cerebral cortex, hyperkinetic dysarthria[1] and "intermittently harsh and strain-strangled" phonation are often present.[2] In Parkinson's disease, a sporadic disorder with degeneration of nigrostriatal pathways, hypokinetic dysarthria and phonation that is "reduced in loudness, breathy and tremulous" predominate.[1,2]

There are insufficient data on the laryngeal pathophysiology responsible for the phonatory disruptions observed in these diseases; however, based on the traditional approach,[1,2] which generalizes characteristics of limb pathophysiology to laryngeal function, one could predict distinct vocal characteristics for these diseases. This approach is summarized in Table 1.

Patients with myotonic dystrophy often have myotonia, weakness, and wasting of muscles.[11] Although the myotonia results from a sarcolemmal defect, other structural changes in muscle fibers, including variation in fiber size, probably account for the patients' weakness and wasting.[12] Electromyographic (EMG) recordings from limb musculature reveal spontaneous repetitive discharges (myotonia) and reduced size of muscle action potentials, indicating loss of fibers within a motor unit.[12] These observations could be generalized to laryngeal muscles to explain the "weak, monotonous"[11] voices observed in these patients by hypothesizing that weakness or myotonia would curtail the normal range of

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TABLE 1. TRADITIONAL APPROACH TO NEUROLOGIC VOICE DISORDERS[1,2]

Neurologic Disease	*Type of Dysarthria*	*Observed Limb Pathophysiology and Predicted Laryngeal Pathophysiology*	*Perceptual Characteristics of Voice*
Myotonic dystrophy	Flaccid	Muscular weakness, wasting, myotonia	"Weak, monotonous"[11]
Huntington's disease	Hyperkinetic	Random twitches, jerks	"Intermittently harsh, strain-strangled"[2]
Parkinson's disease	Hypokinetic	Tremor, rigidity, akinesia	"Tremulous, reduced in loudness, breathy"[2]
Amyotrophic lateral sclerosis	Mixed	Atrophy, weakness, fibrillations, fasciculations	"Wet hoarse"[2]

laryngeal muscle contractions and thereby reduce vocal frequency and intensity ranges.

Patients with HD have chorea: random, involuntary bursts of motor unit activity at rest that result in twitches or jerks and excessive recruitment of motor units during voluntary movements.[13] Although the cause of this disease remains unknown, recent findings reveal selective depletion of neurotransmitter agents such as γ-aminobutyric acid (GABA) in the striatum.[14] Atrophy in the caudate, putamen, and striopallidal nerve fiber bundles probably results in release of pallidal and thalamic activity.[14] These clinical features could be generalized to laryngeal muscles to explain the "intermittently harsh, strain-strangled"[2] voices observed in these patients by hypothesizing random, relatively large laryngeal adductory forces during phonation.

Patients with Parkinson's disease have tremor, rigidity, akinesia, and postural instability that result from dopamine depletion in the nigrostriatum.[14] Studies of extremities suggest difficulty initiating, sustaining, or shutting down individual motor units.[13] Units recruited with more than minimal muscle contraction often tend to fire in small groups at tremor frequency.[13] If generalized to the laryngeal musculature, these characteristics could explain the "tremulous, reduced in loudness and breathy"[2] voices that have been observed.

It is expected that patients with these distinct neural subsystem diseases will present distinct acoustic characteristics of voice.

Diagnosis of Progressive Degeneration. The speech and voice abnormalities in amyotrophic lateral sclerosis (ALS) consist of mixed (flaccid and spastic) dysarthria and "wet hoarse" phonation (Table 1).[1,2,11] In this adult disorder, which is more common after the age of 50, death results in the majority of patients within 3 years.[15] The symptoms vary according to the site of involvement within the cortex, brain stem, spinal cord, and corticospinal tract. Muscular atrophy, weakness, and fasciculations result from degeneration of lower motor neurons, and spasticity develops with corticospinal tract degeneration.[14,15]

Difficulty in speaking is common in advanced ALS and may be an initial symptom in 25% of cases.[15] Although perceptual reports[16] document vocal deterioration with disease progression, no objective acoustic data exist to substantiate this involvement. It is expected that acoustic analysis of phonation will reflect the deterioration in laryngeal function that parallels progression of the disease.

Diagnosis of Subclinical Manifestations. As in all dominantly inherited disorders, the risk of a child of a patient with HD acquiring the disease is 50%.[17] Unfortunately, clinical manifestations do not appear until after childbearing years, and there is no accurate test available for preclinical detection of the abnormal gene.[17] It has been suggested, "Given the hereditary nature of the disease, the motor abnormalities must be present in nascent form long before the usual age of diagnosis in the twenties or thirties."[18] Abnormalities of single motor unit (SMU) control have been measured in the first dorsal interosseous muscle (a finger muscle) of 88% of HD patients and 55% of subjects at risk. Patients with HD could not achieve SMU control, and bursts of chorea were frequent. In individuals at risk, small, irregular, ballistic activations of motor units, termed microchorea, were observed, as well as excessive recruitment of SMUs associated with voluntary activity. It was proposed that microchorea and the inability to sustain SMU firing might be physiologic markers for HD in subjects at risk but without clinical signs.[18]

It is probable that the bursts of chorea observed in the interosseous muscles also occur in the laryngeal musculature. Such activity is one reasonable physiologic correlate for the percepts of "irregular pitch fluctuations and voice arrests" observed in the phonation of HD patients.[19] Similarly, it is possible that subtle motor abnormalities may occur in the laryngeal musculature of individuals at risk that could be reflected in acoustic measures of voice.[19]

METHODS

Subjects. To study the role of acoustic analysis in the diagnosis of diseases of different neural subsystems, subjects with the following diseases were studied: myotonic dystrophy (n = 6), HD (n = 8), and Parkinson's disease (n = 8). Five patients with myotonic dystrophy were men, and one was a woman. They ranged in age from 16 to 61 years (mean, 34 years). Four patients with HD were men, and four were women. They ranged in age from 33 to 66 years (mean, 47 years). All eight patients with Parkinson's disease were men. They ranged in age from 56 to 77 years (mean, 65 years). Patients from

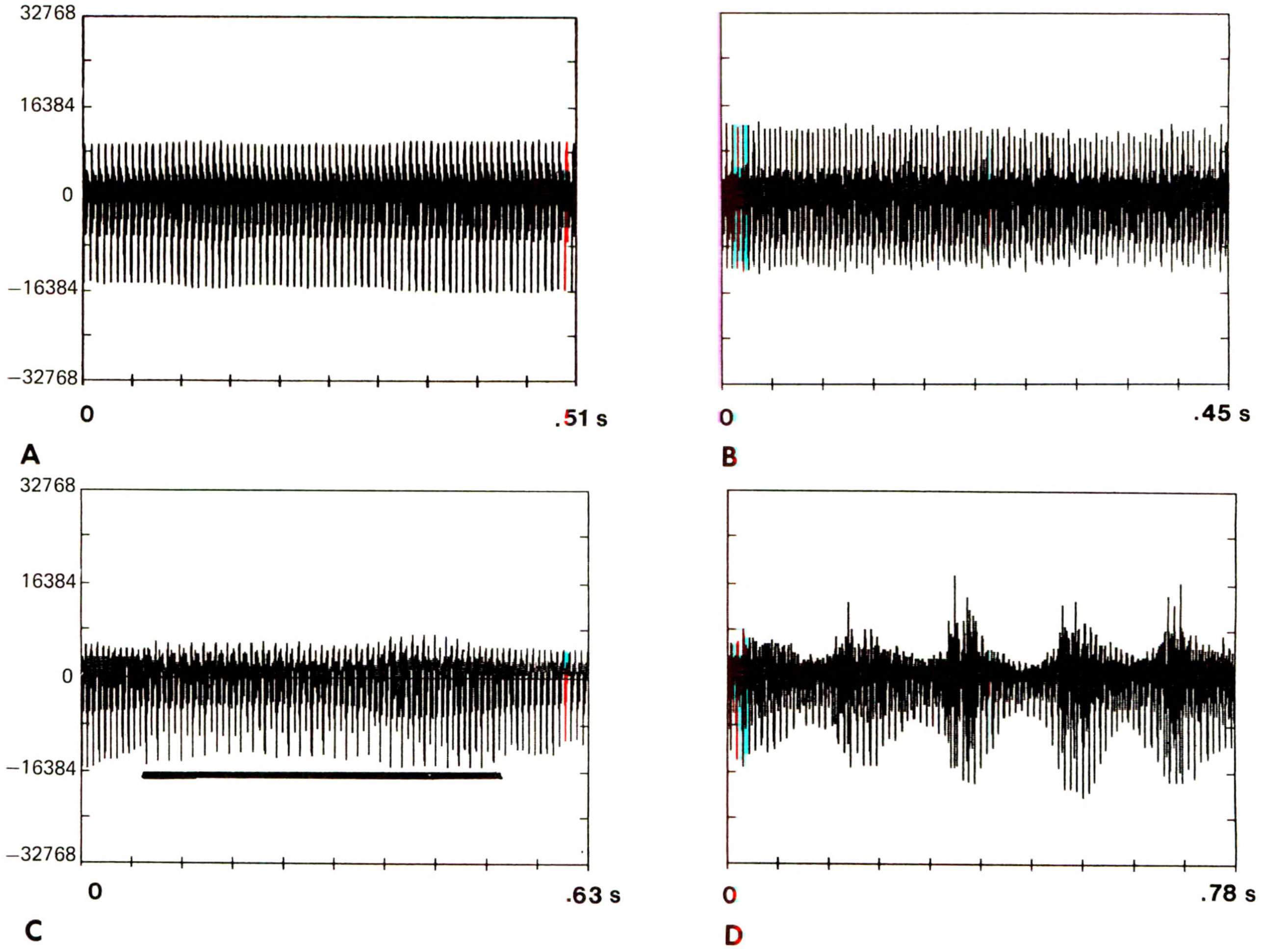

Fig 1. Microphone pressure as function of time for four cases of sustained vowel phonation. Pressure is scaled to maximum range of 16-bit analog to digital converter. Time windows vary from case to case, with tic marks dividing displayed time into ten equal segments. A) Normal speaker. B) Patient with myotonic dystrophy. C) Patient with Huntington's disease. D) Patient with Parkinson's disease. Note irregularity in amplitude of adjacent spikes (pitch pulses) for diseased patients. This suggests irregularity in vocal fold vibration. Horizontal bar in C represents region where low frequency segments are observed.

these groups were selected because they had distinct neural diseases and dysarthrias that included disordered phonation. All patients in these groups presented disordered voices, as evaluated by a speech pathologist. The voices of these patients were described as "mildly hoarse, nasal" (myotonic dystrophy), "having abrupt terminations, pitch drops and vocal fry" (HD), and "hoarse, rough and tremorous" (Parkinson's disease).

To study the role of acoustic analysis in the measurement of disease progression, one 69-year-old man with ALS was studied over a 6-month period. A patient with ALS was selected for this longitudinal study because of the rapid progression of the disease and the well-established concurrence of dysarthria, including dysphonia. The patient was diagnosed as having ALS in March 1981. At the initiation of voice data collection (June 1982) and at the termination of voice data collection (November 1982), the patient was free of bulbar symptoms on neurologic examination. Perceptually, his voice was within normal limits at the initiation of the study and inconsistently "wet hoarse" and "tremorous" at the termination of the study, as reported by a speech pathologist.

To study the role of acoustic analysis in the diagnosis of subclinical manifestations of neurologic disease, 20 symptom-free subjects at risk for HD were studied. Six were men and 14 were women. They ranged in age from 22 to 62 years (mean, 35 years). The voices of all these subjects were reported to be perceptually within normal limits by a speech pathologist.

A control group of 78 subjects with no personal or family history of neurologic disease was also studied. Because aging and gender have been reported to affect voice characteristics,[20,21] this control group was divided into three subgroups in order to approximate the age and sex distributions of the various patient groups. Control group 1 included 48 men ranging in age from 25 to 75 years (mean, 51 years). Data from this control group were compared to data from patients with myotonic dystrophy and HD. Control group 2 was a 16-member subgroup of control group 1; these men ranged in age from 60 to 75 years (mean, 68 years). Data from this control group were compared to data from the older men with Parkinson's disease and the older man with ALS. Control group 3 included 30 subjects, five men and 20 women, ranging in age from 21 to 62 years (mean, 35 years). Data from this group were compared to data from the younger men and women at risk for HD.

Procedures. Subjects were seated in a sound-treated booth (IAC-401-A) and fitted with a headband that suspended a condenser microphone (Sony EMC-21) 15 cm in front of the lips. Voice signals were recorded by a tape recorder (Sony TC-277-4) located outside the booth. Recording level settings on the tape recorder were constant throughout data collection.

Among other tasks, each subject was asked to sustain the vowel /a/ (ah) for "as long as possible" at a comfortable frequency and intensity level. The same procedure was repeated using the vowels /i/ and /u/. All vowels were repeated three times. The entire task was repeated, with subjects sustaining vowel phonation for a comfortable length of time. These specific vowels were selected because they represent extremes of vocal tract configuration. Sustained vowel phonation was selected because it facilitated interpretation of phonatory function by reducing the coarticulatory effects accompanying connected speech, and it required minimal subject training. Subjects practiced this task until the experimenter determined performance limits had been achieved.

Recordings were analyzed in two ways. Initially, a running analysis was made of oscillographic output of these voice signals (Seimans jet-spray oscillograph). To allow discrete visualization of waveforms, hard copy waveform data were displayed at 20 cm/s (men) and 40 cm/s (women). This allowed visual inspection of all sustained phonation data. Based on this visual inspection, representative sections of phonation were sampled from approximately the midsection of these vowels and digitized at 20,000 samples per second. The midsection of vowels was selected for analysis in order to reduce the effects of phonatory onset and offset. Digitized samples did not include the low frequency segment sections previously identified in the sustained phonation of patients with HD.[19] Acoustic analyses were carried out using the voice analysis program GLIMPES[22] to measure the following variables, which have been reported to be sensitive to phonatory instability: fundamental frequency, shimmer, jitter, and harmonics-to-noise ratio. Fundamental frequency is the number of vocal fold vibratory cycles per second. Jitter and shimmer refer to cycle-to-cycle variations in frequency (or period) and amplitude, respectively. Harmonics-to-noise ratio reflects the relationship between the amount of periodic energy and noise per unit of time.[23] Greater phonatory instability has been associated with increases in jitter and shimmer[20,24] and decreases in harmonics-to-noise ratio.[23] Formulas for these acoustic measures are summarized in the following equations.

Perturbation factors, with linear trend:

$$PF = \frac{100\sum_{i=2}^{N}\left|x_i - x_{i-1}\right|}{(N-1)\bar{x}}$$

Perturbation factors, without linear trend:

$$PF = \frac{100\sum_{i=2}^{N-1}\left|.5\,(x_{i+1}+x_{i-1})-x_i\right|}{(N-2)\bar{x}}$$

Harmonics-to-noise ratio[23]:

$$H/N = N\int_0^T f_A^2(t)\,dt \Big/ \sum_{i=1}^{N}\int_0^{T_i}\left[f_i(t)-f_A(t)\right]^2 dt$$

where:

$$f_A(t)=\sum_{i=1}^{N}\frac{f_i(t)}{N}$$

The tabled data reflect a minimum of 1 second of sustained phonation sampled from each patient's steadiest maximum-duration /a/ phonation.

RESULTS AND DISCUSSION

Diagnosis of Diseases of Different Neural Subsystems. Sustained vowel phonation data from one patient representing each disease group are presented in Fig 1B-D for comparison with a control (normal) subject (Fig 1A). Visual inspection of these data reveal different vocal patterns for each patient. Relatively large cycle-to-cycle disruptions in amplitude (shimmer) are apparent in the irregular waveforms of the myotonic voice (Fig 1B). In contrast, the data from the HD patient (Fig 1C) reveal an abrupt phonatory disruption, rather than cycle-to-cycle deviancies. This is shown as an octave drop in fundamental frequency over 30 cycles and then a return to the original fundamental frequency. The voice of the Parkinson's disease patient (Fig 1D) reveals rhythmic amplitude tremor imposed upon cycle-to-cycle deviancies.

The values for the perturbation measures (shimmer, jitter, harmonics-to-noise ratio) are presented in Table 2. Although individual myotonic patients had increased shimmer and jitter and decreased harmonics-to-noise ratios when compared to individuals in control group 1, inspection of group data revealed that the increased jitter values were most apparent. Patients with myotonic dystrophy had mean jitter values (both with and without linear trend) that were three times greater than were observed in subjects in control group 1. In this report,

TABLE 2. ACOUSTIC MEASURES OF SUSTAINED VOWEL PHONATION PRODUCED BY PATIENTS WITH MYOTONIC DYSTROPHY, HUNTINGTON'S DISEASE, AND PARKINSON'S DISEASE AND TWO CONTROL GROUPS

	Fundamental Frequency (Hz)		*Shimmer (%)*		*Jitter (%)*		*Harmonics-to-Noise Ratio (dB)*	
	$\bar{x}$	*SD*	$\bar{x}$	*SD*	$\bar{x}$	*SD*	$\bar{x}$	*SD*
Myotonic dystrophy (n = 6)	137	33	2.43 (1.90)	1.63 (1.46)	1.46 (1.27)	1.70 (1.49)	20.28	4.97
Huntington's disease (n = 8)	170	33	2.27 (1.58)	0.87 (0.78)	0.68 (0.34)	0.52 (0.22)	16.35	1.88
Parkinson' disease (n = 8)	128	16	5.18 (3.43)	2.02 (1.45)	1.26 (1.05)	0.29 (0.35)	14.75	2.97
Control group 1 (n = 48)	126	21	1.98 (1.51)	1.02 (0.87)	0.53 (0.45)	0.24 (0.22)	24.72	2.78
Control group 2 (n = 16)	125	27	2.43 (1.86)	1.23 (1.15)	0.56 (0.46)	0.22 (0.21)	24.07	1.98

Data in parentheses have had linear trend removed.

relatively large jitter values reflect large cycle-to-cycle variations in period of the acoustic output pressure. Period variations may depend largely upon the integrity of the muscles governing vocal fold elasticity (VFE). We suggest that the relatively large values of jitter for the myotonic dystrophy patients result from a large cycle-to-cycle instability of the VFE system as a consequence of general laryngeal muscular weakness and/or myotonia.

Polyphasic motor unit action potentials of reduced duration (1 to 3 ms) have been reported in dystrophic limb muscles.[25] These observations were attributed to a loss of fibers that resulted in a decrease in both voltage amplitude and the contribution of distant fibers, as well as slight asynchrony. We hypothesize that such activity in laryngeal VFE systems may be the pathophysiologic correlate for the acoustic observations. These acoustic observations support earlier perceptual work that classified the voice disorder of myotonic patients as a "relatively constant" disorder.[2(p89)]

In contrast, the phonatory disruption observed in the HD patients did not reflect as much cycle-to-cycle laryngeal involvement. Although the shimmer and jitter values of the HD patients were within normal limits during undisrupted phonation, voices of these patients were characterized by abrupt drops in frequency of approximately one octave (low frequency segments; incidence will be discussed below).[19] Drops in frequency such as these may depend upon the muscles governing VFE. Random, inappropriate bursts of motor unit activity 0.1 to 1 second in duration have been observed in choreic limb muscles. We suggest that such choreiform involvement in laryngeal muscles is sufficient to affect the vibratory characteristics of the vocal folds, causing a fundamental frequency drop of approximately one octave. The low values of the harmonics-to-noise ratio without high values of jitter and shimmer suggest vocal tract changes that alter the waveform of the acoustic signal. This may correspond to choreiform involvement in articulatory musculature. These acoustic observations support earlier work that classified the voice disorder of patients with HD as an "arrhythmically fluctuating" disorder.[2(p107)]

Compared to control group 2, the patients with Parkinson's disease had greater shimmer and jitter values (by a factor of two) and a smaller harmonics-to-noise ratio (almost half). The relatively large shimmer and jitter values reflect large cycle-to-cycle variation in amplitude and period, respectively, of the acoustic output pressure. Amplitude variation may depend largely on the laryngeal adductory-abductory muscular system integrity, because of the associated control over glottal flow waveform characteristics (and therefore the associated intensity generation at the laryngeal level). Period variation may depend largely upon the integrity of the muscles governing VFE. Inspection of these data with linear trend removed (Table 2) suggests that the increased cycle-to-cycle phonatory instability reflected in these measures may be related in part to an apparent phonatory tremor (Fig 1D). Four of the eight patients with Parkinson's disease studied presented perceptible vocal tremor. The frequency of tremor in limbs of the patients with Parkinson's disease has been reported to be 4 to 7 Hz.[14] The vocal tremor observed here was within that range (5 to 7 Hz). These findings are consistent with earlier perceptual work that classified patients with Parkinson's disease as having a "rhythmically fluctuating neurologic voice disorder."[2(p76)]

The frequency of vocal tremor in the patients with Parkinson's disease was near the frequency of vibrato observed in the singing voice, as well as that of the fluctuations of pitch in patients with spastic dysphonia.[26] We can only speculate on the exact mechanism underlying these voice characteristics. Limb tremor is produced by alternating or synchronous activity in antagonistic muscles. The frequency of limb tremor oscillation has been related to a potential central tremor generator, a peripheral stretch reflex response, and the mechanical properties of the oscillating structure.[27] The thalamus and the cerebellum have been proposed as central sources for tremor. Because of the relatively consistent fre-

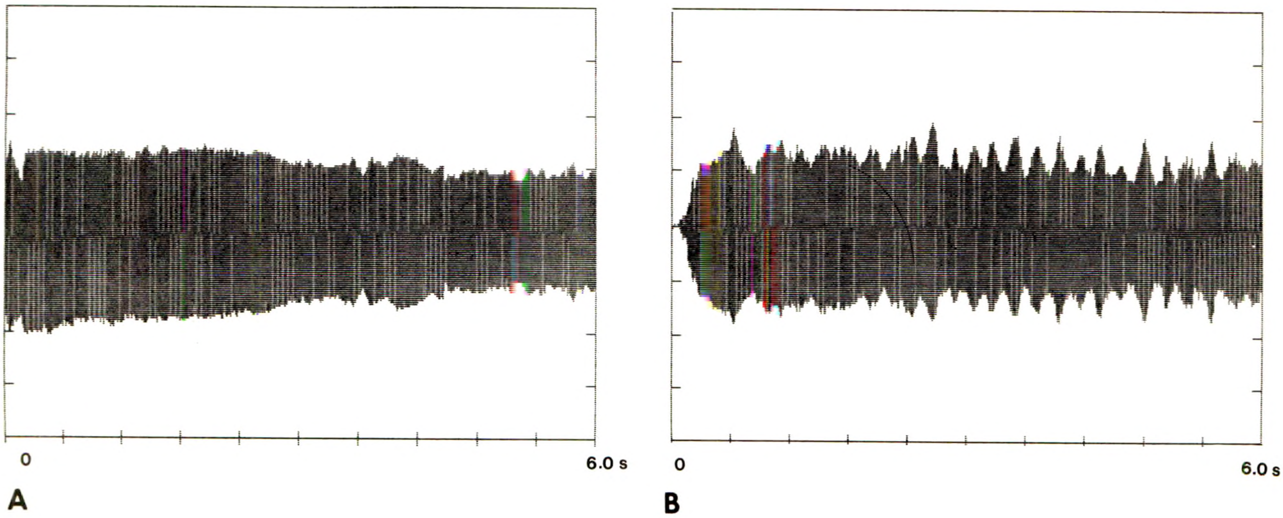

Fig 2. Approximately 6 seconds of sustained vowel phonation produced by patient with amyotrophic lateral sclerosis. A) Initial recording. B) Six months after initial recording.

quency of 5 to 6 Hz for both vocal tremor and vibrato, one could propose a similar central generator, which in the case of patients is released from suppression by disease and in the case of singers is selectively recruited. This is consistent with the hypothesis[26] that singers are able to inhibit periodic neural signals coming through the recurrent laryngeal nerve to both the adductors and abductors of the larynx, while at the same time allowing pulses that are transmitted through the superior laryngeal nerve to the cricothyroid to manifest themselves as frequency modulation. It should be pointed out that whereas vibrato typically has been reported to be a frequency oscillation, the vocal tremor observed in these patients with Parkinson's disease was related to both frequency and amplitude oscillation.

These preliminary data from patients with myotonic dystrophy, HD, and Parkinson's disease add support to the hypothesis that patients with distinct neural subsystem diseases would present distinct acoustic characteristics of voice. These findings encourage future research, which must expand these preliminary studies in order to determine their representativeness.

Diagnosis of Systemic Degeneration in Neurologic Disease. The possible contribution of acoustic voice analysis to the diagnosis of systemic degeneration is exemplified by a study of a patient with ALS. Fig 2A is a sample of sustained vowel phonation from a patient with ALS at the beginning of the 6-month period of data collection, and Fig 2B is a sample of sustained vowel phonation at the end of this period. An increase in phonatory instability is apparent at the end of the 6-month period, as reflected by the increased amplitude variation (Fig 2B).

Quantification of these differences is presented in Table 3 and is illustrated graphically in Fig 3. Dates of trials 1 through 4 were June, July, August, and November, respectively. Data in Table 3 represent the average of one sample (1 second) from each of three maximally sustained /a/ vowels for each of the four trials. Shimmer and harmonics-to-noise ratio were most sensitive to deterioration in phonatory function in this patient. Shimmer increased from 2.18% (SD = 0.48) in trial 1 to 3.33% (SD = 1.77) in trial 4. The harmonics-to-noise ratio decreased from 21.74 dB (SD = 1.74) in trial 1 to 16.59 dB (SD = 3.53) in trial 4. Shimmer and harmonics-to-noise ratio were 2.43% (SD = 1.23) and 24.07 dB (SD = 1.98), respectively, in control group 2. These acoustic data document an increase in phonatory instability in trial 4 of the ALS patient that exceeds the range of control group 2.

TABLE 3. ACOUSTIC MEASURES OF SUSTAINED VOWEL PHONATION PRODUCED BY PATIENT WITH AMYOTROPHIC LATERAL SCLEROSIS AND CONTROL GROUP

	Patient With Amyotrophic Lateral Sclerosis									
	Trial 1		*Trial 2*		*Trial 3*		*Trial 4*		*Control Group 2*	
	$\bar{x}$	*SD*	$\bar{x}$	*SD*	$\bar{x}$	*SD*	$\bar{x}$	*SD*	$\bar{x}$	*SD*
Fundamental frequency (Hz)	145.00	3.68	153.00	3.47	174.00	2.48	162.00	2.83	125.00	27.00
Shimmer (%)	2.18 (1.67)	0.48 (0.42)	1.34 (1.03)	0.11 (0.07)	3.33 (1.39)	1.43 (0.48)	3.33 (2.13)	1.77 (1.23)	2.43 (1.86)	1.23 (1.15)
Jitter (%)	0.44 (0.34)	0.04 (0.04)	0.32 (0.27)	0.04 (0.05)	0.27 (0.23)	0.06 (0.05)	0.49 (0.36)	0.22 (0.18)	0.56 (0.46)	0.22 (0.21)
Harmonics-to-noise ratio (dB)	21.74	1.74	23.29	1.32	17.21	2.52	16.59	3.53	24.07	1.98

Data in parentheses have linear trend removed.

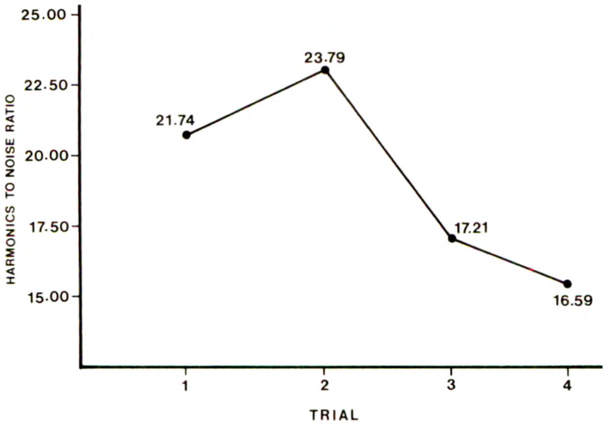

Fig 3. Harmonics-to-noise ratio measured four times over 6-month period from patient with amyotrophic lateral sclerosis.

Although a decline in phonatory stability is apparent from these acoustic measures, no bulbar symptoms were observed by repeated neurologic examinations during this 6-month interval. One could speculate that during this time period, degenerative changes had occurred in bulbar motor neurons innervating laryngeal musculature, but that this degeneration had not reached a point of clinical significance.

These preliminary data support the hypothesis that acoustic analysis of phonation reflected deterioration that accompanied neuronal degeneration in this patient. In addition, they support the sensitivity of acoustic analysis in reflecting early bulbar symptoms before they were clinically observed. Given the heterogeneity of patient groups, longitudinal studies such as this may offer a particularly useful approach to studying the relationship between neurologic disease and voice.

Diagnosis of Subclinical Manifestations of Neurologic Disease. Figure 4 displays low frequency segments observed in patients in the earliest stages of HD (Fig 4A) and in one fourth of the individuals we studied who were at risk for HD (Fig 4B). The incidence of these low frequency segments in HD patients (n = 8), individuals at risk (n = 20), and control group 3 (n = 30), given as the ratio of the number of low frequency segments to the number of vowel prolongations studied, was as follows: HD patients, 102/27 (378%); individuals at risk, 34/90 (36%); and control group 3, 9/270 (3%). These data were obtained from visual inspection of hard copy waveform representations of nine sustained vowel phonations for each of the individuals in the control group, four or five sustained vowel phonations for individuals at risk, and three or four sustained vowel phonations for patients with HD.

Inspection of the low frequency–segment data reveals that for the subjects at risk, the incidence of low frequency segments was approximately 12 times as great as that observed in the normative control group. Individual data reveal that five of the 20 subjects at risk presented these low frequency segments. The occurrence of low frequency segments in these five subjects ranged from five to nine per subject.

These preliminary findings support the hypothesis of increased phonatory instability in certain individuals at risk for HD. The observation of low frequency segments in these individuals extends the continuum of phonatory disruption in HD[19] to include certain individuals at risk. Although the laryngeal pathophysiology responsible for these observations could be microchorea, it is premature to speculate until more extensive analyses are carried out.

Furthermore, the significance of such vocal abnormalities in individuals at risk for HD can be determined only relative to their carrier status. The recent genetic marker findings[28] soon may allow identification of carrier status in these individuals at risk. Analysis of phonation in individuals with known car-

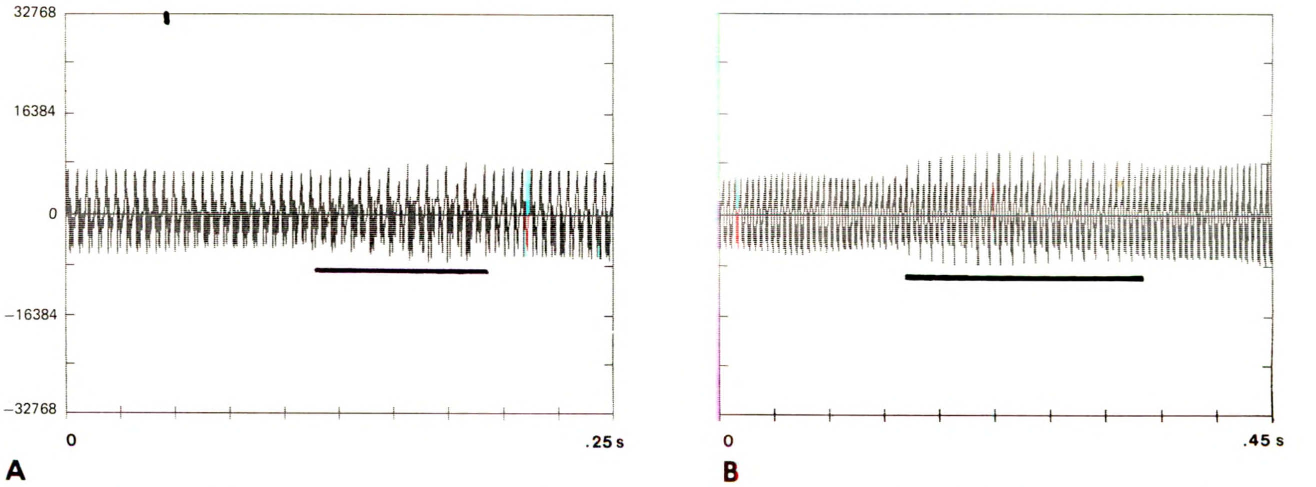

Fig 4. Sustained vowel phonation produced by A) patient with Huntington's disease and B) individual at risk for Huntington's disease. Bar — low frequency segments.

rier status would offer a unique potential for evaluating the significance of such vocal abnormalities.

CONCLUSION

Preliminary data presented in this report suggest that voice analysis of neurologically diseased patients may make important contributions to early and differential diagnosis and to the measurement of disease progression.

Future research on the neurologically diseased voice must take into consideration a number of theoretical and practical issues. The establishment of relationships among phonatory characteristics and site or progression of neurologic disease depends upon precise definition of neuropathology. Adequate medical and pharmacologic information is necessary for valid data interpretation. Furthermore, categorization within disease group by stage of disease and cause may reduce within-group heterogeneity and facilitate more meaningful observations. For the same reason, the categorization of control groups of individuals should include chronologic age and vocal use.

Tasks for study also must be selected carefully. We must examine the validity of generalizing from the results of nonmeaningful sustained vowel phonation to phonatory characteristics in meaningful speech. Recent observations suggest that laryngeal behavior may differ significantly between such tasks.[29] Future research must examine laryngeal tasks that are diagnostically efficient and accurate.

Acoustic variables should be expanded as well. Although the cycle-to-cycle variables such as jitter and shimmer may offer valuable information about short-term phonatory instabilities, study of the neurologically diseased voice may require quantification of longer-term phonatory instabilities. For example, the low frequency segments observed in the voices of patients with HD[19] and the amplitude tremor observed in the voices of patients with Parkinson's disease may provide valuable information about patients' neurolaryngeal pathophysiology that may not be apparent in cycle-to-cycle measures.

Analysis procedures must be carefully selected. The aperiodicity of many neurologically diseased voices may prevent the use of automatic computer analysis on all but the most periodic segments of voice. Thus, the representativeness of data from automatic computer analysis must be a consideration.

For patients with movement disorders, acoustic data can be obtained simply, noninvasively, and relatively inexpensively. Additional levels of measurement such as electroglottography, EMG, and aerodynamic measures may also be useful.

Traditionally, it has been suggested[1,2] that the laryngeal pathophysiology responsible for phonatory involvement in patients with neurologic disease was consistent with limb pathophysiology. Recent work, however, suggests that "assessments of motor speech disorders that assume a common pathophysiology for the limbs and the speech motor subsystems are likely to be in error."[30] Such findings must be considered when developing hypotheses and interpreting phonatory data.

Future research will allow consideration of the preceding theoretic and practical issues in the study of phonation in patients with neurologic disease.

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ACUTE EFFECTS OF IRRADIATION ON MIDDLE EAR MUCOSA

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Single field, fixed irradiation of bilateral tympanic cavities using 200-kV x-rays was administered to five guinea pigs. The irradiation dose was 30 Gy. They were killed immediately after irradiation, and bilateral middle ear mucosa was examined for ciliary activity and epithelial structure. Significant deterioration of the ciliary activity in the middle ear mucosa was observed, proximal as well as distal to the eustachian tube. Electron microscopy showed various changes in the irradiated middle ear mucosa. The most conspicuous findings were hyperreactivity in secretion, vacuolation of ciliated cells, and stomal edema.

KEY WORDS — ciliary activity, electron microscopy, middle ear mucosa, irradiation.

INTRODUCTION

It has been reported by many authors that irradiation has a serious influence upon the mucociliary system of the respiratory mucosa.[1-4] A number of studies also have laid emphasis on the effects of irradiation on the function and structure of the inner ear.[5-8] Changes induced in the middle ear mucosa, however, have received little consideration. The

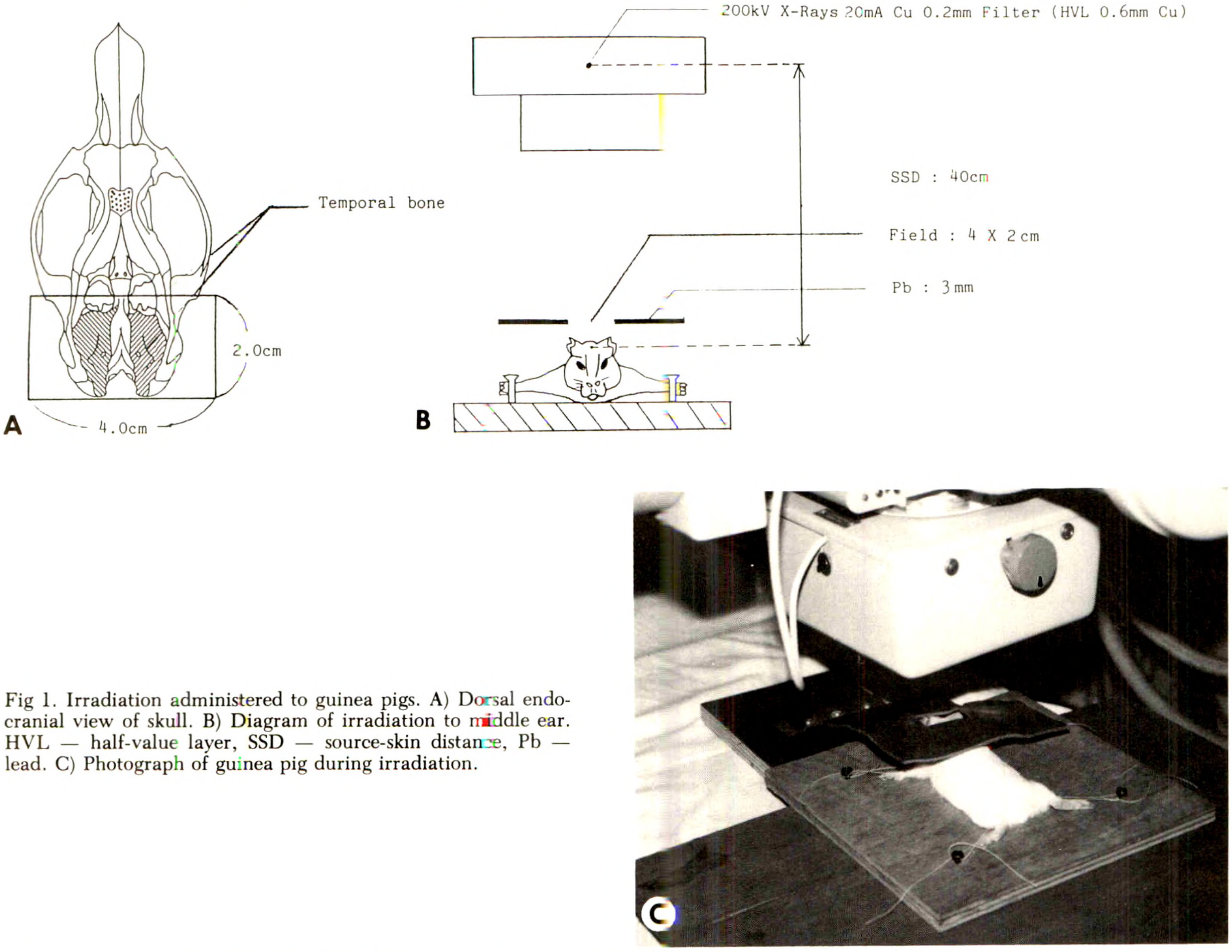

Fig 1. Irradiation administered to guinea pigs. A) Dorsal endocranial view of skull. B) Diagram of irradiation to middle ear. HVL — half-value layer, SSD — source-skin distance, Pb — lead. C) Photograph of guinea pig during irradiation.

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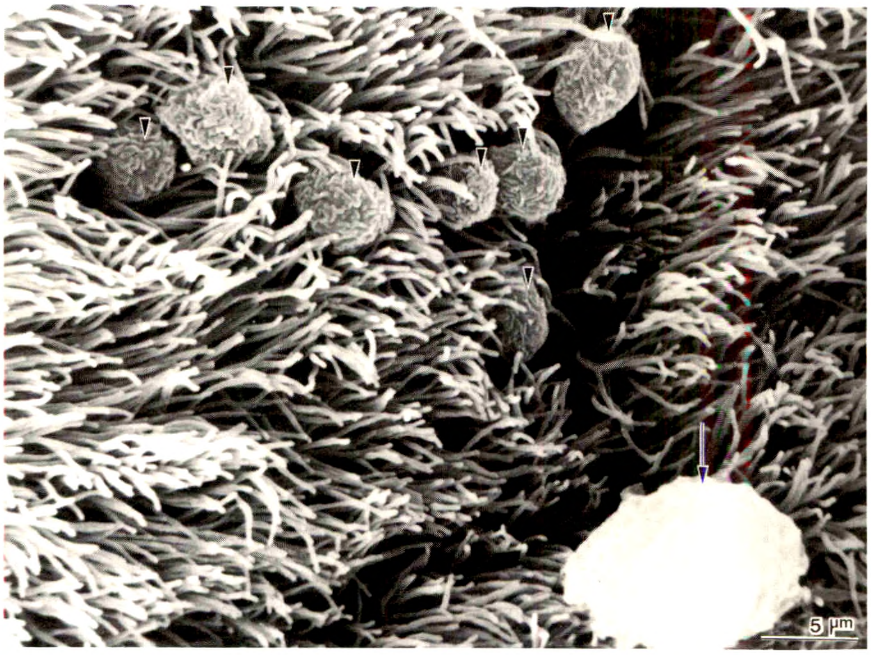

Fig 2. Scanning electron microscopic picture of proximal mucosa of irradiation group showing abundant cilia, sporadic ballooning of goblet cells (arrowheads), and large mass of secretory granules (arrow).

present study was designed to examine the acute effects of irradiation on the mucociliary system of the middle ear lining.

MATERIALS AND METHODS

Nine healthy guinea pigs (250 g) were used in this study; four of the nine served as control animals, and the remaining five received irradiation. First, radiographic examination of the head was performed to establish an irradiation field of about 4 x 2 cm in size, of which the center was placed in accord with bilateral middle ear regions. The irradiation group was anesthetized with Nembutal and fixed to prevent movement during irradiation. Single field, fixed irradiation of bilateral tympanic cavities was performed using 200-kV x-rays and a 0.2-mm copper filter (half-value layer, 0.6 mm). The irradiation dose was 30 Gy (Fig 1). The guinea pigs were

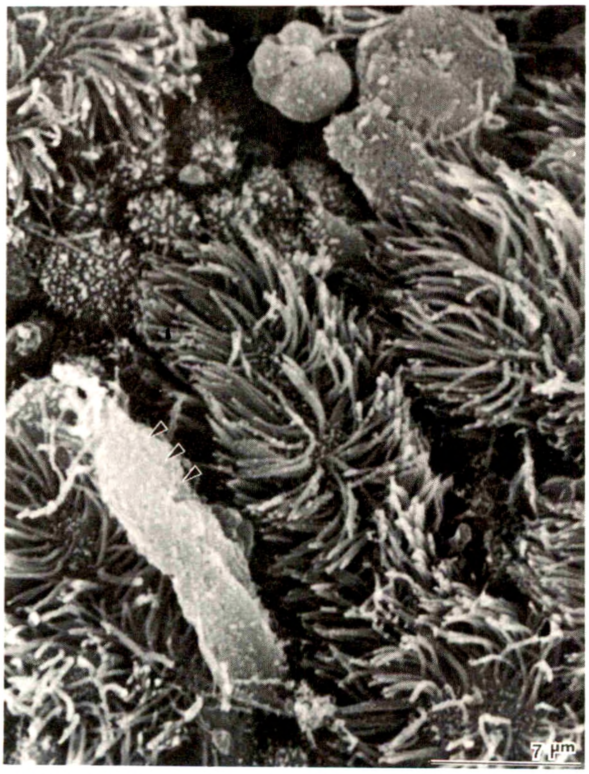

Fig 3. Scanning electron microscopic picture of proximal mucosa of irradiation group showing sporadic falloff of epithelial cells (arrowheads).

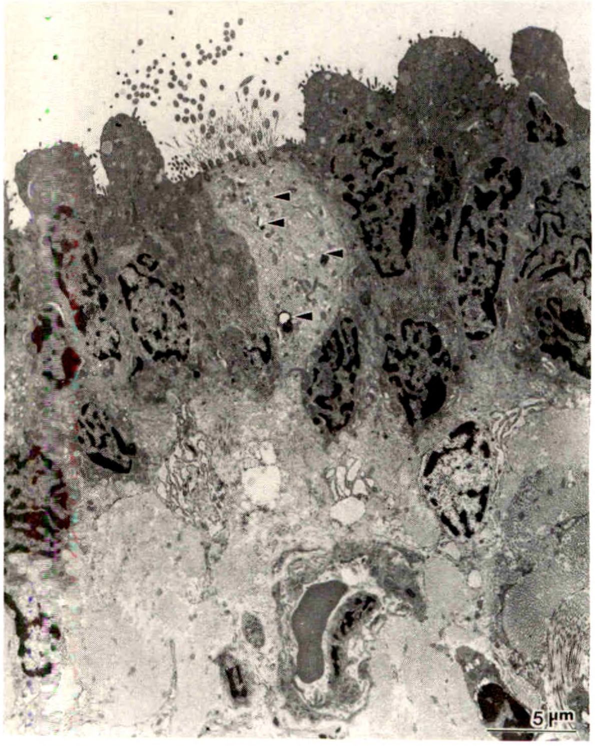

Fig 4. Transmission electron microscopic picture of proximal mucosa of irradiation group showing goblet cells filled with abundant secretory granules and small vacuoles (arrowheads) in cytoplasm of ciliated cells.

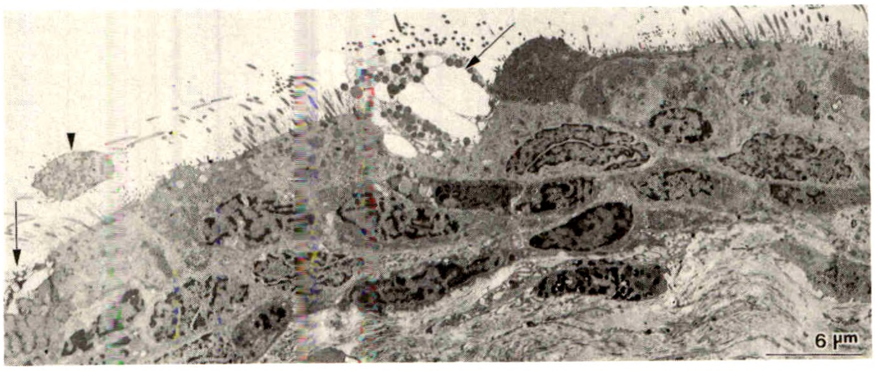

Fig 5. Transmission electron microscopic picture of proximal mucosa of irradiation group showing goblet cells (arrows) after expulsion of masses of secretory granules. Arrowhead — expulsion toward lumen.

decapitated immediately after irradiation, and bilateral middle ear mucosal samples from two sites (middle ear mucosa close to the tubal orifice [proximal mucosa] and middle ear mucosa more distal to the orifice [distal mucosa]) were obtained from each of the five animals. The samples obtained from the right tympanic bullae were used for examination of ciliary activity (beats per minute) and those from the left ones for electron microscopy. The ciliary activity was examined at six locations in each site of each of the five samples in a physiologic saline solution at an ambient temperature of 30°C using the direct and quantitative photoelectric method of Ohashi and Nakai.[9,10] Samples for electron microscopy were immersed immediately in 2.5% cold glutaraldehyde in 0.1 *M* phosphate buffer solution and fixed for 2 hours. They were transferred to a buffer solution for washing and postosmicated by 2% osmium tetroxide in the same buffer. After dehydration in ethanol, some of them were critical point dried, coated with gold, and then observed under an S-405 scanning electron microscope. The remainder were embedded in epoxy resin after dehydration. Ultrathin sections were made with an ultratome and examined under an H-300 transmission electron microscope.

Four animals of the control group also were anesthesized, put into the same holder in the same room, left there for the same amount of time after anesthesia, and treated as the experimental group was, except that the off-on switch was not thrown to administer irradiation. They were decapitated, and right middle ear mucosal samples from two sites (proximal and distal) were obtained from each animal. The samples obtained were examined for ciliary activity (beats per minute) according to the same photoelectric method.

RESULTS

GROSS EXAMINATION

On gross examination, no effusion or congestion was observed in the tympanic cavities of the control group. No effusion and moderate congestion were observed in each tympanic cavity of the irradiation group.

CILIARY ACTIVITY AND STRUCTURE OF MIDDLE EAR MUCOSA

Proximal Mucosa. Ciliary activity (mean ± standard deviations [SD]) in the proximal mucosa of the

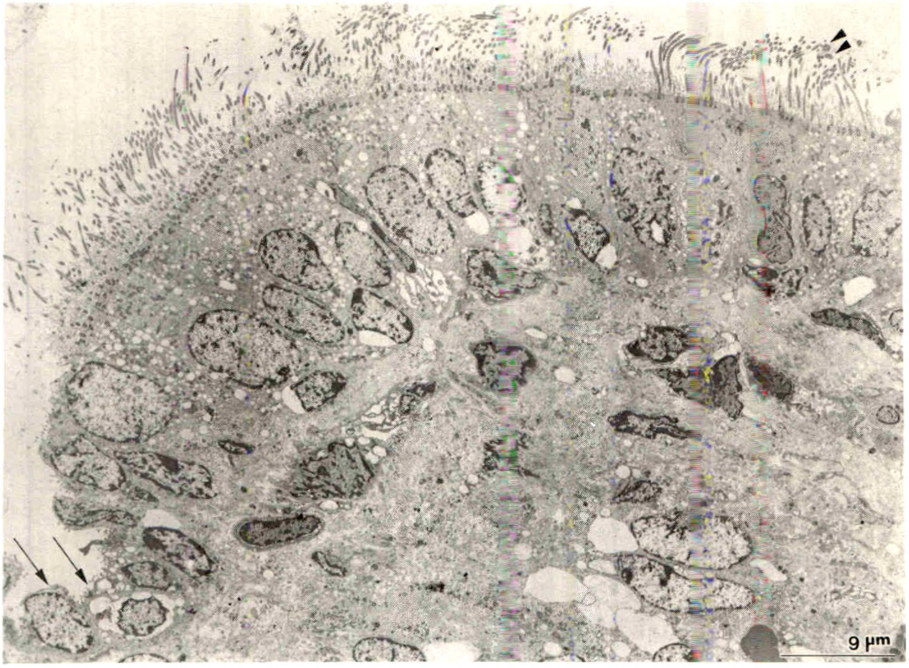

Fig 6. Transmission electron microscopic picture of proximal mucosa of irradiation group showing marked vacuolation of ciliated cells, sporadic secretory droplets (arrowheads) adhering to tips of cilia, thickening of subepithelial layer, and sporadic exposure of basal cells (arrows) due to falloff of epithelial cells.

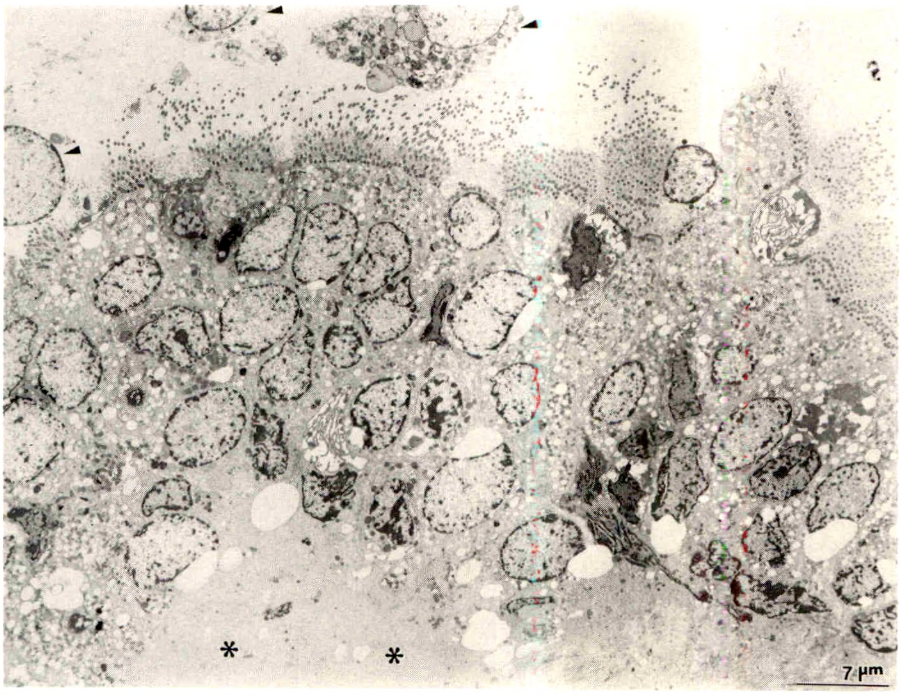

Fig 7. Transmission electron microscopic picture of proximal mucosa of irradiation group showing marked vacuolation of ciliated cells, sporadic cell debris in lumen side (arrowheads), and stomal edema (asterisks).

four controls was 786 ± 46, 762 ± 39, 752 ± 56, and 788 ± 48 beats/min, respectively. On the other hand, the respective ciliary activity (mean ± SD) of the five animals of the irradiation group was 466 ± 53, 497 ± 47, 517 ± 55, 446 ± 42, and 472 ± 49 beats/min. The level of ciliary activity of the irradiation group was statistically smaller than that of the control group ($p < .01$).

Many cytoplasmic protuberances of goblet cells and sporadic secretory droplets on cilia were observed in the proximal mucosa of the irradiation group (Fig 2). Few changes were observed in the cilia, but falloff of ciliated cells was observed sporadically by scanning electron microscopy (Fig 3). Transmission electron microscopy showed hypersecretion including ballooning of goblet cells (Fig 4) and a mass of secretory droplets (apocrine secretion) on the cilia (Fig 5). Few disordered cilia such as compound cilia were observed, but marked vacuolation and sporadic falloff of epithelial cells were observed in most of the samples examined (Figs 6 and 7). In addition, moderate thickening of the subepithelial layer, probably due to edema, also was observed (Fig 7).

Distal Mucosa. Ciliary activity (mean ± SD) in the distal mucosa of the four control animals was 937 ± 42, 918 ± 48, 935 ± 29, and 897 ± 48 beats/min, respectively, and that of the five animals of the irradiation group was 524 ± 59, 539 ± 62, 527 ± 55, 487 ± 64, and 482 ± 61 beats/min, respectively. The level of ciliary activity of the irradiation group was statistically smaller than that of the control group ($p < .01$).

Scanning electron microscopy showed cytoplasmic protuberances of nonciliated cells and falloff of sporadic epithelial cells (Fig 8A). Sporadic rupture of basement membrane and falloff of epithelial cells also were observed in the distal mucosa of the irradiation group by transmission electron microscopy (Fig 8B).

DISCUSSION

The function and structure of the tubotympanum have been the subject of much controversy. Ojala[11] stated that the middle ear mucosa consisted of flat or cuboidal epithelial cells that lacked secretory functions. A number of recent electron microscopic investigations, however, have established that the middle ear lining, as well as the other respiratory epithelia, has a mucociliary system composed of ciliated cells, secretory cells, and a mucous blanket.[12-17] Sadé[18] has demonstrated, by tracing the movement of foreign materials placed on the mucosa, that the middle ear mucosa has an active transport function. Our recent study using a photoelectric method has confirmed that this clearance is carried out by cilia.[19,20] We have established in these studies that ciliary activity varies depending upon its location within the tubotympanum of normal guinea pigs: ciliated cells are more active in the area distal to the eustachian tube than at the eustachian tube or in the transitional area, and the more distal the site of examination, the stronger the ciliary activity. We also have demonstrated the involvement of some pathologic factors in dysfunction of cilia in the tubotympanum.[21,22]

The influence of irradiation on the function and structure of the respiratory mucosa has been well studied.[1-4] Although the middle ear mucosa has function and structure similar to those of the respiratory mucosa, little has been elucidated about the

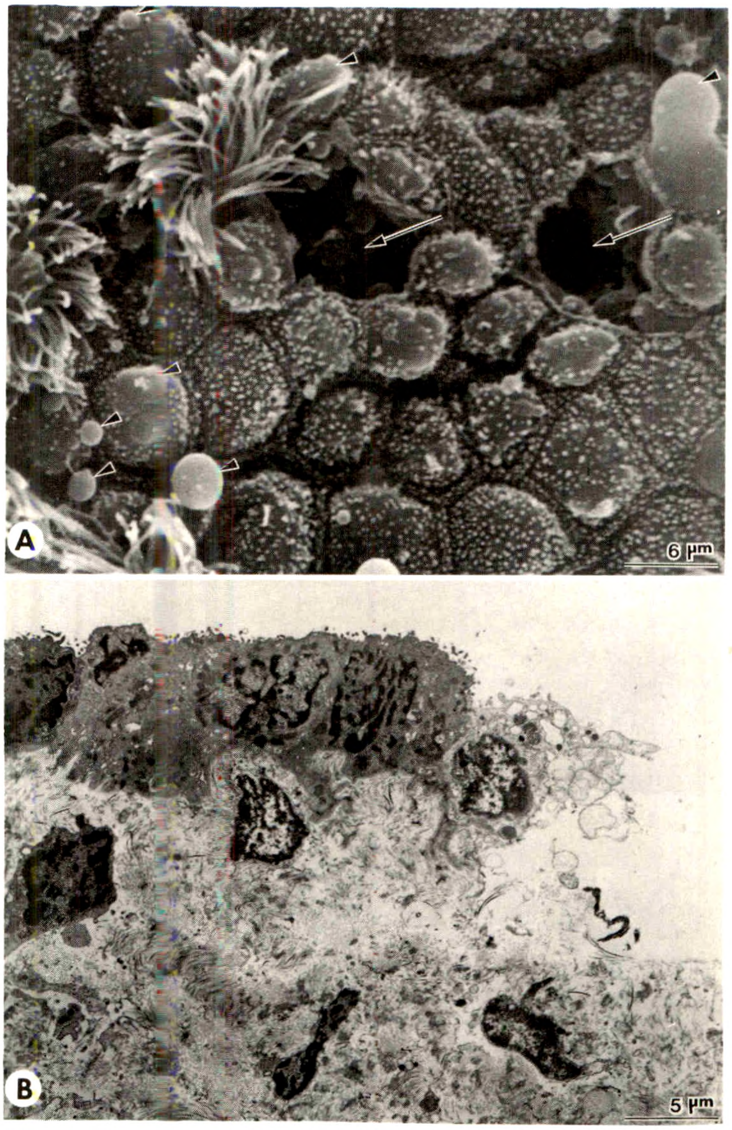

Fig 8. Scanning electron microscopic pictures of distal mucosa of irradiation group. A) Sporadic cytoplasmic protuberances of nonciliated cells (arrowheads) and sporadic falloff of epithelial cells (arrows). B) Sporadic falloff of epithelial cells and sporadic rupture of basement membrane.

effects of irradiation on the middle ear. Borsanyi et al[8] demonstrated mucositis, desquamation, and edema in the acute stage. Mass[23] termed this process radiation otitis media. In the chronic stage, Berg and Linggren[7] observed epithelial atrophy and fibrosis in the middle ear mucosa. Recently, Elwany[24] has observed by electron microscopy the irradiation-induced changes in the middle ear mucosa of six patients who developed conductive hearing loss 6 to 11 months after receiving a total dose of 6,500 to 8,500 rad for the treatment of head and neck malignancies not involving the temporal bone: the epithelium showed marked reduction of the cytoplasmic mass, variable degrees of ciliary loss, and widening of the intercellular spaces with disruption of some maculae adherentes. These studies have shown that irradiation has acute and chronic effects on the structure of middle ear mucosa.[7,8,23,24]

On the other hand, however, the effects of irradiation on the ciliary activity in the middle ear mucosa have never been discussed except in our recent study,[22] in which we studied irradiation-induced changes in ciliary activity of the tubotympanum in an in vitro model. The cilia of the eustachian tube and middle ear mucosa showed different reactions to irradiation according to their tympanic locations. To be more precise, the ciliary activity of the middle ear mucosa around the orifice of the tube increased following irradiation with 3.0 Gy or less, and decreased after irradiation with 4.0 Gy or more, but the ciliary activity from a site distal to the tube decreased with small doses of irradiation.

The present study has focused on the acute effects of irradiation on the function and structure of middle ear mucosa using an in vivo laboratory model. Significant deterioration of the ciliary activity in the middle ear mucosa, proximal as well as distal to the tube, was observed immediately after irradiation with 30 Gy. Scanning electron microscopy showed various changes in the irradiated middle ear mucosa. The most conspicuous findings were hyperactivity of goblet cells, vacuolation of ciliated cells, and stomal edema. These findings were somewhat similar to those of otitis media with effusion.[25-29] In this study we did not find middle ear effusions, but the possibility cannot be excluded that otitis media with effusion may occur in the chronic stage. For complete understanding of the effects of irradiation on the middle ear, further investigations are needed into its chronic and recurrent effects.

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ADDUCTOR SPASTIC DYSPHONIA: HETEROGENEITY OF PHYSIOLOGIC AND PHONATORY CHARACTERISTICS

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Physiologic and phonatory characteristics of 23 subjects with adductor spastic dysphonia were studied, including examination of the laryngeal appearance by fiberoptic nasoendoscopy, neurologic examination, and measurement of phonatory airflow and speaking fundamental frequency. These characteristics displayed considerable heterogeneity among the subjects investigated. Three patterns of laryngeal appearance during phonation were observed: vocal fold adduction, associated ventricular fold constriction, and approximation of the laryngeal inlet. Eight of 13 subjects demonstrated some neurologic abnormality. For the majority of subjects, the airflow demonstrated marked variability during sustained phonation; for different subjects, this variability was observed to be associated with either an oscillatory or irregular airflow pattern. The modal speaking fundamental frequency for the women and men with adductor spastic dysphonia was not significantly different from that for age- and sex-matched controls.

KEY WORDS — airflow, fundamental frequency, larynx, spastic dysphonia, vocal cords.

INTRODUCTION

Adductor spastic dysphonia is an enigmatic voice disorder that is generally unremitting and unresponsive to symptomatic therapy. It is recognized by a strained, groaning, staccato, effortful voice.[1-3] Most of the earlier authors suggested, or accepted, that adductor spastic dysphonia was a psychoneurotic disorder.[4-6] This view has since been challenged.[7-10] After extensive investigation, Aronson[2] proposed that adductor spastic dysphonia is a heterogeneous disorder with neurologic, psychogenic, and idiopathic subtypes — a view that suggests a differential approach to treatment decisions. Also implicit in the concept of a heterogeneity of causes is that subjects with adductor spastic dysphonia may display different physiologic or phonatory characteristics, which could be of diagnostic value.

Measurement of the average expiratory airflow during phonation has been employed in previous investigations of abnormal voice[11,12] and may be a useful technique in the clinical evaluation of adductor spastic dysphonia. Phonatory airflow is considered to be controlled by the glottal resistance and expiratory force,[11] and a low airflow during phonation suggests a high glottal resistance. Hirano et al[12] measured phonatory airflow during sustained vowels in a variety of vocal disorders, including that in eight subjects with adductor spastic dysphonia, and observed that the mean airflow for each of these subjects did not exceed the normal range (43 to 222 mL/s) established in the same study. Briant et al[13] reported, however, that the (group) mean phonatory airflow in sustained phonation for nine subjects with adductor spastic dysphonia was very low, at 29.3 mL/s. It is possible that the difference in the data presented by each group of authors may have resulted from inclusion of different clinical subtypes. Other authors have applied techniques such as longtime average spectra[14] or spectrographic analysis[15,16] in attempts to quantify the acoustic characteristics of adductor spastic dysphonia. Although the terms "low pitch" and "monotone" have been used in descriptions of adductor spastic dysphonia,[1,9] these observations do not appear to have been quantified by analysis of speaking fundamental frequency.

In order to investigate the possibility of heterogeneity in adductor spastic dysphonia, we have examined 23 adults (seven men and 16 women) with this disorder, none of whom had been treated by recurrent laryngeal nerve section such as that reported by Dedo and Izdebski.[17] All subjects were examined by indirect laryngoscopy. Speaking fundamental frequency was measured and compared with age- and sex-matched control subjects. For some subjects, subsequent examinations included fiberoptic nasoendoscopy (15 subjects), neurologic examination (13 subjects), and phonatory airflow assessment (20 subjects).

METHODS

Subject Selection. Diagnosis of adductor spastic dysphonia in 23 subjects was made following the

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TABLE 1. LARYNGEAL APPEARANCE AND AIRFLOW IN ADDUCTOR SPASTIC DYSPHONIA

Subject	Years Since Onset*	Phonatory Adduction			Airflow Pattern†	Mean (mL/s)	SD (mL/s)	MPT (s)
		VF	Vent	Inlet				
F1	3	+	+	(+)	Oscillating	80.8	25.8	4.4
F2	3				Oscillating	84.5	54.7	16.2
F3	(8)	+	(+)		Oscillating	84.5	28.9	11.7
F4	(6)	+			Oscillating	71.8	101.0	18.5
F5	2.6	+			Irregular	246.5	152.4	5.4
F6	(15)				Irregular	58.5	39.3	15.8
F7	(5)	+			Irregular	72.0	63.0	10.6
F8	(10)				Irregular	46.8	18.4	24.2
F9	(13)	+	+	+	Irregular	78.4	103.9	21.1
F10	(9)	+	(+)		Irregular	72.2	92.2	11.4
F11	2	+			Irregular	99.0	21.3	8.0
F12	(22)	+	(+)		Steady	54.3	4.1	9.3
F13	1	+			Steady	184.0	15.1	13.4
F14	(4)	+			Steady	33.5	5.6	9.9
					Mean	90.5		
					SD	56.8		
M1	3.3	+	+	+	Irregular	34.0	18.9	26.1
M2	1				Irregular	53.8	33.5	19.9
M3	1.5	?	?	+	Irregular	38.8	12.3	19.6
M4	(4)	+	(+)		Irregular	149.3	32.7	25.8
M5	1.3				Steady	39.5	5.0	19.4
M6	2.6	+			Steady	147.5	20.5	17.2
					Mean	77.2		
					SD	55.6		

Subject F5 exhibited irregular airflow pattern throughout most of phonatory attempt, including 2-second period analyzed; however, brief intermittent periods of oscillatory airflow pattern were apparent in other sections of record.

VF — vocal folds, Vent — ventricular folds, Inlet — aryepiglottic folds and epiglottis, + — phonatory adduction, (+) — inconstant phonatory adduction, ? — constriction of laryngeal inlet obscured observation of ventricular and vocal folds during phonation, SD — standard deviation, MPT — maximum phonation time.

*Shown in parentheses when estimated by subject.

†Mean airflow measured over 2-second period selected from sample of maximally sustained phonation of vowel /ah/ at comfortable pitch and intensity.

perception of a strained, groaning, staccato, effortful voice quality independent of the presence of dysarthria. These subjects were referred by otolaryngologists following indirect laryngoscopy over a 5-year period; they are designated by number in Tables 1 and 2. The age range was 21 to 79 years (average, 66 years for women and 39 years for men), with a female to male ratio of 2.4 to 1. The duration of the disorder varied from approximately 1 to 22 years. Matched control subjects for the speaking fundamental frequency analysis were hospital staff members for younger subjects, and orthopedic hospital patients for subjects 65 and older. None of these control subjects had any history of voice or speech disorders.

Otolaryngologic and Neurologic Examinations. Subsequent evaluations were undertaken of those of the 23 subjects who could be recalled for additional examination. Fifteen subjects were examined with both a mirror and a flexible transnasal fiberscope; the latter permitted observation of the larynx during continuous speech and during vowel prolongation at the subject's usual speaking pitch. Thirteen subjects were given a standard, detailed neurologic examination. Laboratory investigation included full blood count ESR; biochemical screening; syphilis serology; determination of ceruloplasmin, vitamin B12, and folate levels; and a computed tomographic scan of the head with and without contrast medium.

Phonatory Airflow. Average airflow during sustained phonation was measured in a conventional manner[11,12] as the differential pressure developed across a fixed resistance using a Fleisch pneumotachograph and Hewlett Packard models 270 differential pressure transducer, 8805 B carrier amplifier, and 7754B 4-channel pen recorder. A microphone was built into the respiratory face mask (Vacumed model 15226), and after low pass filtering of the rectified acoustic signal, the average magnitude was displayed as a signal of voicing occurrences and an index of the relative speaking intensity. A microphone was coupled to the neck, and the fundamental frequency contour derived from the vibratory waveform (see below) was displayed. Observation of these signals ensured that airflow measurements were not carried out at extremes of the patient's fundamental frequency or intensity range. Subjects sustained the vowel /ah/ at a comfortable pitch and intensity for their maximum phonation time. Airflow was measured manually at 100- or 200-ms intervals, depending on the paper speed selected during testing, over a 2-second period from the onset of phonation after allowing a 2-second settling period (Fig 1), since it is known that the onset phase of airflow is associated with considerable var-

TABLE 2. COMPARISON OF SPEAKING FUNDAMENTAL FREQUENCY IN ADDUCTOR SPASTIC DYSPHONIA SUBJECTS AND CONTROL SUBJECTS

	Age	*Modal Fo*	*Habitual Range* *ST*	*Habitual Range* *Hz*	*% Low*
Spastic Dysphonia Subjects					
F1	61	95	31.8	35-220	54.4
F2	59	170	9.9	130-230	46.5
F3	69	180	30.7	45-265	78.2
F4	73	185	14.1	135-305	38.3
F5	66	130	15.6	75-185	60.9
F6	79	135	13.0	85-180	62.3
F7	54	175	26.4	50-230	81.8
F8	63	160	31.9	50-315	68.2
F9	68	210	19.0	100-300	67.4
F10	78	150	24.0	50-200	79.2
F11	75	145	21.9	65-235	68.5
F12	61	190	31.0	50-300	74.5
F13	61	155	12.0	120-240	36.7
F14	38	210	29.7	55-305	78.1
F15	74	142	14.5	95-220	46.2
F16	73	155	22.7	85-315	45.8
Mean	66	162	21.8*		61.1*
SD	10	30	7.9		15.1
M1	52	115	25.2	50-215	57.1
M2	21	160	11.5	100-195	70.4
M3	35	175	15.0	105-250	58.7
M4	36	115	12.0	85-170	44.2
M5	42	140	8.8	105-175	56.8
M6	64	140	23.3	65-250	57.1
M7	23	90	7.0	70-105	61.4
Mean	39	134	14.7		58.0
SD	15	29	7.0		7.7
Control Subjects					
CF1	58	190	11.1	150-285	36.9
CF2	59	160	8.6	125-205	50.0
CF3	69	170	8.4	135-220	46.4
CF4	71	155	15.9	100-250	47.5
CF5	65	175	13.7	125-275	42.3
CF6	79	185	17.6	105-290	55.7
CF7	53	195	11.4	155-300	34.8
CF8	64	165	11.3	120-230	48.7
CF9	69	140	9.0	110-185	46.7
CF10	78	190	10.6	135-250	55.7
CF11	76	130	17.4	75-205	54.6
CF12	60	195	9.3	155-265	43.0
CF13	62	200	12.8	150-315	39.1
CF14	38	190	13.2	135-290	44.7
CF15	73	175	16.2	110-280	49.4
CF16	72	185	8.4	135-220	64.3
Mean	65	175	12.2		47.5
SD	11	21	3.2		7.7
CM1	52	105	9.3	85-145	39.8
CM2	22	125	8.6	100-165	44.2
CM3	35	100	9.1	80-135	42.9
CM4	36	100	14.9	70-165	41.9
CM5	42	85	14.9	55-130	50.3
CM6	64	105	17.8	50-140	71.9
CM7	22	120	8.1	100-160	38.3
Mean	39	106	11.8		47.1
SD	15	13	3.9		11.6

F0 — speaking fundamental frequency, ST — semitones, % Low — percentage of F0s within habitual range that were lower than modal F0.

*p<.01.

iability.[18] The mean airflow and its variation (SD) were calculated.

Speaking Fundamental Frequency. Speaking fundamental frequency was measured during the reading of the whole Rainbow Passage. Vibrations of the pretracheal skin were detected in the midsagittal plane using a dynamic microphone coupled to the neck by a rubber cuff. The signal was continuously monitored on a storage oscilloscope (Tektronix T912) and processed by a pitch meter, which extracted the fundamental period from the acoustic signal by a peak-picking method; pulses at the laryngeal vibratory frequency were provided to a microcomputer (Motorola 6800 based). Speaking fundamental frequency was measured by a program that measured the period of alternate vocal cycles (resolution, 10 μs) and accumulated a running total of the time spent at frequencies from 20 to 500 Hz in 5 Hz increments. The reliability of the system has been described previously.[19] The modal speaking fundamental frequency (fundamental frequency with the greatest probability of occurrence) and habitual range (corresponding to the range of fundamental frequencies encompassing the middle 96% of the modal amplitude) were recorded from the displayed distribution. Semitones (ST) were calculated from fundamental frequency (Fo) values as

$$ST = \frac{\log F_0 - \log 16.35}{\log \sqrt[12]{2}}$$

A Student's *t* test for paired comparisons was used for statistical analysis.

RESULTS

Otolaryngologic Examination. The form and range of movement of the vocal folds during respiration was normal in 14 subjects with adductor spastic dysphonia; the remaining subject (F5) exhibited a tremor of the vocal folds on expiratory adduction. During speech, three predominant patterns of laryngeal or vocal tract closure during voice arrests were observed for the 15 subjects (Table 1). In seven cases (F4, F5, F7, F11, F13, F14, M6) vocal cord adduction alone was responsible for the inappropriate interruptions to continuous speech and, in two cases (F4, F5), for the tremor that was evident. Four other subjects (F3, F10, F12, M4) exhibited associated, periodic adduction of the ventricular folds, either along the full length or, for one subject (F10), only anteriorly. For one of these subjects (F3) a synchronous tremor of the vocal and ventricular folds was observed. The remaining subjects exhibited more extensive constriction of the vocal tract; three (F9, M1, M3) displayed regular glottic and supraglottic closures, and for one subject (F1), these signs were occasionally apparent. The supraglottic closures consisted of ventricular fold adduction, and in addition, there was episodic and erratic apposition of the epiglottis to the aryepiglottic folds. In one subject (M3) this approximation

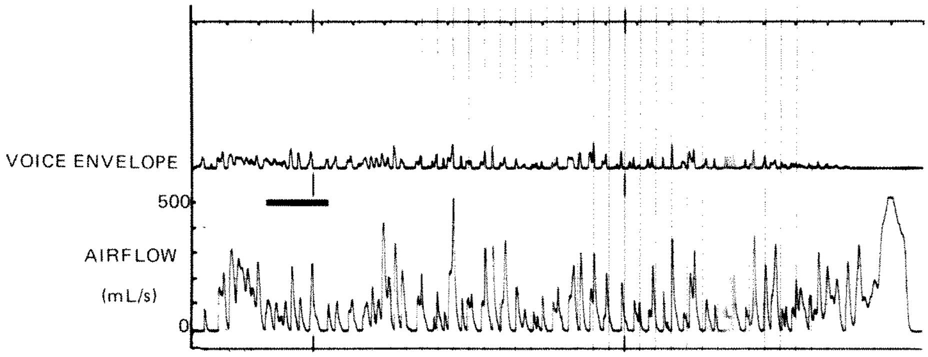

Fig 1. (Subject F9) Irregular type phonatory airflow pattern in adductor spastic dysphonia. Traces represent, from top to bottom, time (1-second marker), average magnitude of acoustic signal (voice envelope), and expiratory airflow recorded during maximally sustained phonation of vowel /ah/ at comfortable pitch and intensity. Two-second period indicated by bar illustrates period for which measurement of airflow was made for each subject.

was so complete and consistent as to effectively prevent observation of the ventricular and vocal folds during phonation at any time. The larynx in this case was elevated and the epiglottic lid remained closed, reminiscent of the swallowing position. Accompanying this there may have been some simultaneous lower pharyngeal constriction. Three of the subjects in this latter group (F9, M1, M3) were judged perceptually as among the more severely impaired in our group. Voice arrests were accompanied by tension of the respiratory and facial musculature associated with a considerable effort to communicate.

Neurologic Examination. Neurologic assessment revealed the following abnormalities in eight of the 13 subjects examined. Four (F1, F3, F4, F5) had a benign essential tremor of the voice, with or without tremor of the tongue, head, upper limbs, and handwriting; two (M1, M4) had brisk jaw or facial jerks; three (F4, F7, M1) had a grade II vascular retinopathy; one (M1) had mild cogwheel rigidity on synkinesis of an upper limb; one (F1) had a lid lag and stare (thyroid function normal); and one (F9) had dysphagia (with spoon nails and angular stomatitis) that proved to be due to a pharyngeal web. For the remaining subjects (F11, F12, F13, M3, M5) no abnormality was detected.

Phonatory Airflow. The mean phonatory airflow for 14 women was 90.5 ± 15.2 mL/s (SE), and that for six men, 77.2 ± 23.2 mL/s (Table 1). The phonatory airflow for 15 of 20 subjects was noticeably variable (coefficient of variation, 21.5% to 141%). The pattern of variability appeared to take two predominant forms.

Four women (F1 to F4 inclusive) had a phonatory airflow (mean, 80.4 ± 3.0 mL/s) that demonstrated a tremor at 5 to 7 c/s. The flow generally oscillated from the zero flow level (F3; Fig 2A), but was sometimes superimposed upon a background flow (such as 50 mL/s), and at times both variations occurred within one sample. None of these subjects was able to produce a steady airflow pattern, although the extent of the flow oscillations usually was damped when the subjects were sustaining notes in the falsetto register.

The second type of pattern, observed in 11 subjects, contained irregular fluctuations in phonatory airflow, with zero expiratory airflow levels recorded intermittently. Variations within this group were observed for different subjects. One subgroup was characterized by frequent brief episodes of relatively high airflow (up to 500 mL/s for ≤ 100 ms) interposed upon short intervals (< 200 ms) of diminished

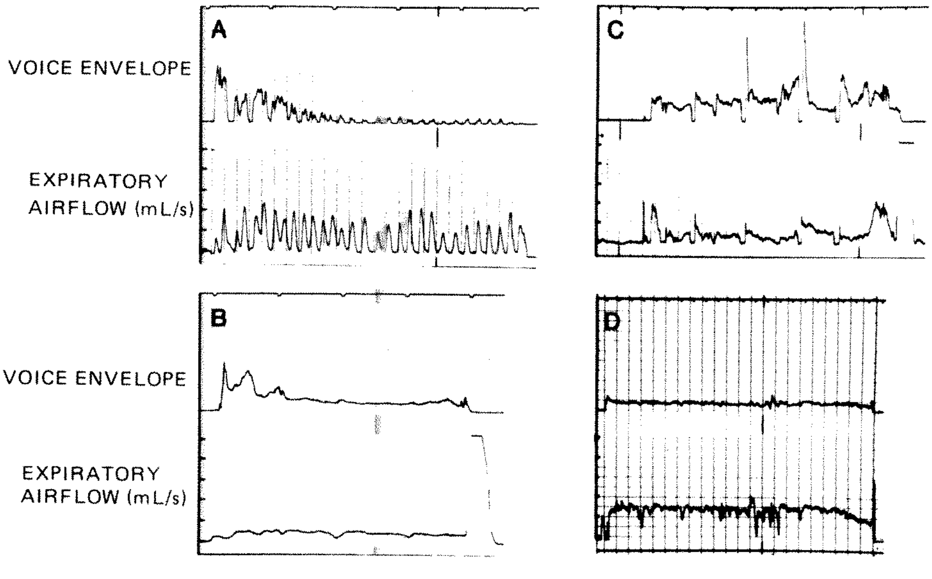

Fig 2. Characteristic patterns of phonatory airflow observed in spastic dysphonia. A) Oscillatory; B) steady; C,D) irregular. Notation as for Fig 1. Calibration of airflow record: A) 200 mL/s/division (1,000 mL/s full scale); B-D) 100 mL/s/division (500 mL/s full scale).

or absent expiratory airflow (F5, F9, F10, M2), as illustrated in Fig 1. A second subgroup was characterized by intermittent periods of zero expiratory airflow and relatively low airflows (F6, F7, M1, M3; Fig 2C). A third subgroup (F8, F11, M4) exhibited a quasi-steady airflow (at 47, 99, and 149 mL/s, respectively) punctuated by brief decreases, and occasionally increases, in airflow (M4; Fig 2D). One subject (M4) in the latter group could, at times, produce a sustained phonation with a normal (ie, steady) airflow pattern. Several other subjects were able to achieve this, but only when attempting falsetto phonation (F7, F8, M1, M2, M3), and two of these subjects (M1, M3) sometimes used falsetto voice to facilitate communication. Three other subjects (F5, F10, F11) who demonstrated an irregular pattern of airflow at habitual speaking fundamental frequency levels exhibited an oscillatory airflow pattern, associated with a tremulous voice, during high-pitched phonation. Two subjects (F6, F9) were unable to achieve a sustained note above 250 Hz because of voice arrests.

The remaining five subjects exhibited a steady (coefficient of variation, 7.5% to 16.8%) airflow pattern (F14; Fig 2B). The mean airflow for these subjects was 91.8 ± 31.5 mL/s, and no episodes of zero expiratory flow occurred during sustained phonation. Four were able to achieve a steady airflow pattern and a normal voice quality when sustaining notes at a higher pitch, although for the fifth subject (F12), sustained notes in the falsetto register often were associated with a tremulous voice and an oscillatory airflow pattern.

Speaking Fundamental Frequency. The average modal speaking fundamental frequency for the women was 161.7 ± 7.6 Hz (SE), and for the men, 133.6 ± 11.0 Hz. The age range of these subjects was 38 to 79 years, and as it is known that speaking fundamental frequency decreases with increasing age,[20] individual results were compared with those for a control group matched for age and sex. For both sexes the results were not significantly different ($p > .05$).

The habitual range of speaking fundamental frequencies, as measured in ST, was greater for both women and men than for their respective controls; for the female group this difference was significant (Table 2). The wider habitual range was observed to be associated with the inclusion of a relatively greater proportion of speaking fundamental frequencies lower than the modal speaking fundamental frequency as depicted in Table 2, on which "% Low" represents the percentage of speaking fundamental frequencies within the habitual range that were lower than the modal fundamental frequency. This index was calculated as

$$\%\ \text{low} = \frac{F_0 - F_1\ (\text{ST})}{F_{\text{total}}\ (\text{ST})} \times 100$$

where F_0 is the modal fundamental frequency, F_1 is the lowest fundamental frequency in the habitual range, and F_{total} is the habitual range. Note that this index is greater for both women and men with spastic dysphonia than for their respective controls. Table 2 also includes fundamental frequency data for three subjects who are not included in Table 1; the times from onset of the disorder were estimated as 14, 1, and 1 years by subjects F15, F16, and M7, respectively.

Additional Observations. Some of these subjects have been observed regularly since the time of initial testing and over this time have demonstrated changes from the results given in Tables 1 and 2. One subject (M3) displayed severe and unremitting symptoms of adductor spastic dysphonia for 18 months, but 6 months after measurement of the results reported here, the spastic dysphonia abruptly resolved, and except for the occasional appearance of a strained quality, a more normal voice has been sustained for several months. When retested, the phonatory airflow had altered from an irregular pattern (38.8 ± 12.3 mL/s) to a steady pattern at 208 ± 1.5 mL/s. The modal speaking fundamental frequency had lowered from 175 to 105 Hz, and the habitual range had decreased from 15 to 12.3 ST. Another subject (F13) experienced perceptual worsening of her adductor spastic dysphonia over 14 months from the time of initial testing. When retested, the speaking fundamental frequency (160 Hz) was similar to the earlier result, although the habitual range had increased from 12 to 14 ST and the proportion of speaking fundamental frequencies lower than the modal speaking fundamental frequency was greater ("% Low" index as defined in Table 2 increased from 37% to 58%). The phonatory airflow was irregular in pattern (42.7 ± 20.5 mL/s), punctuated by periods of absent expiratory flow, in contrast to the earlier result of a steady airflow at 184 ± 15.1 mL/s.

DISCUSSION

It would appear that in these 23 subjects, each with a diagnosis of adductor spastic dysphonia, there are markedly varied characteristics; under the generic label of adductor spastic dysphonia there may well be heterogeneous physiologic characteristics representing different manifestations of the disorder. The laryngeal appearance in adductor spastic dysphonia by fiberoptic nasoendoscopy revealed three somewhat overlapping categories — vocal fold adduction, ventricular and vocal fold adduction, and constriction of the laryngeal inlet — in agreement with previous reports.[21,22] Aronson[2] has suggested that the severity of the disorder may parallel these three categories. The design of this study did not include perceptual judgments on the severity of the symptoms; however, our clinical impressions tend to support this proposal. The three subjects (F9, M1, M3) who consistently exhibited associated constriction of the laryngeal inlet had a severely impaired voice, and conversely, two subjects (F13, M6) were quite mildly impaired (F13 at the time of initial testing; see Results section), and only vocal fold phonatory adduction was observed. Association of symptom severity and the level of laryngeal constriction may not be perfect, however: in one case (F10) phonatory vocal fold adduction was associated with only intermittent approximation of the anterior borders of the ventricular folds, although the symptoms were judged to be severe. As only one otolaryngologic examination was performed on each subject, we cannot be certain that there may not be episodic variation in the laryngeal appearance during phonation.

Following Aronson's[2] proposal that the classification of adductor spastic dysphonia should be made with reference to the suspected cause, ie, neurologic, psychogenic, or idiopathic, we can apply the classification of adductor spastic dysphonia of psychogenic origin for one subject (M3), adopting Aronson's criterion of a dramatic change in a symptom following palliative therapy. This subject's adductor spastic dysphonia resolved following a period in therapy in which he resorted to whispered communication because of the severity of the voice arrests. Four other subjects exhibited signs that suggested that their disorders could have been psychogenically based (F13, F14, M5, M6), but such an association is difficult to apply with confidence. Recent studies have reported the occurrence of concurrent neurologic signs in adductor spastic dysphonia, including facial tics, spasmodic torticollis, essential tremor, and blepharospasm,[8-10,23] as well as abnormalities in auditory brain stem response.[24,25] In the present study, neurologic investigation revealed abnormality in eight of 13 subjects examined. For seven of these, although the neurologic signs were suggestive of CNS involvement, a causal association with the adductor spastic dysphonia is necessarily tentative.

Three patterns of phonatory airflow seemed to emerge: oscillating, irregular, and steady. A degree of correspondênce between laryngeal appearance and phonatory airflow pattern was evident. Five of the eight subjects who exhibited an irregular airflow pattern and for whom laryngeal examination during connected speech was carried out displayed associated phonatory constriction of the ventricular folds or laryngeal inlet. It is possible that some of these examples of irregular phonatory airflow represent the effects of compensatory and extraordinary expiratory forces applied to achieve voice against firmly adducted glottal and supraglottal structures. As the voices of four of these subjects were judged as severely impaired (see above), it is possible that the need for such compensatory efforts may increase with symptom progression. On the other hand, in three of the four subjects who displayed a steady airflow pattern and were examined by nasoendoscopy, vocal fold adduction only was observed on phonation. It may have been that the vocal folds were hyperadducted in these and other subjects, but the physical signs to be expected in such cases are unclear. Although the airflow patterns reported here were observed on repeated tests on each subject at the time of testing, as for our observations of laryngeal phonatory appearance, the possibility of episodic variation cannot be ruled out. Indeed, we observed a dramatic change in phonatory airflow for two subjects when they were retested some months later, although in these cases the different airflow patterns paralleled a pronounced change in symptom severity. Although the data are limited, we suggest that measurement of phonatory airflow might provide an indication of the severity of adductor spastic dysphonia that could be useful when surgical treatments are envisaged or when charting temporal changes.

For five subjects (F1 through F5) the voice disorder was classified as adductor spastic dysphonia of essential tremor.[2,26] Although the voice sounded strained and forced, there was a characteristic tremor of 5 to 7 c/s. Four of these subjects exhibited an oscillatory type of airflow pattern, and the fifth subject (F5) displayed both irregular and oscillatory airflow patterns at different times (Table 1). It may be that this variation between the two types of patterns is also associated with the use of compensatory maneuvers designed to inhibit the involuntary tremulous movements of the vocal folds.[27] Our finding that the respiratory movements of the vocal folds in this subject were tremulous confirms earlier reports.[22,28] Active inspiratory dilation and expiratory constriction of the vocal folds occur in response to neural commands from brain stem respiratory neurons,[29] and our finding indicates that the disordered motor control in adductor spastic dysphonia may extend to these unconscious events.

Airflow during sustained vowel phonation for four of 21 subjects was found to be lower than the (critical) normal range of 43 to 222 mL/s established by Hirano et al.[12] Only one subject exhibited a greater mean airflow, and this result was associated with marked variability (coefficient of variation, 62%). In general, our data support the finding of Hirano et al[12] that adductor spastic dysphonia is not necessarily associated with abnormally low phonatory airflow. That we detected a small number of subjects with a low airflow, whereas Hirano et al[12] did not, may be due to the larger number of subjects in our sample. It is difficult, however, to reconcile our findings with those of Briant et al,[13] who found an extremely low (group) mean phonatory airflow. A novel finding in the present study was that the variability of the airflow during sustained phonation in adductor spastic dysphonia was striking. For many of our subjects the coefficient of variation was high, approaching unity in some cases — a finding that suggests that measurement of phonatory airflow that relies on averaging procedures, without attention to airflow variability, may be difficult to interpret in spastic dysphonia.

Although the speaking fundamental frequency for the subjects was not significantly different to that of age- and sex-matched controls, two men in our group had speaking fundamental frequencies that were higher than the normal male range[19] and may have been adopted by these subjects in their need to communicate. In this respect, the mean male speaking fundamental frequency (133.6 Hz) may include such compensatory behaviors and as such may not be representative of the typical man with adductor spastic dysphonia.

Probably the most striking finding specific to fundamental frequency data is the wide habitual range that seemed to characterize many subjects. Such frequency variability is at some variance with the literature reports of a monotonic voice as one prominent characteristic of adductor spastic dysphonia. For the women the habitual range in STs was significantly greater than that of age- and sex-matched controls, and this was related to the inclusion of a relatively greater proportion of low speaking fundamental frequencies. This finding may at least in part account for the perception of low pitch and perhaps the strained vocal quality in adductor spastic dysphonia. These lower speaking fundamental frequencies, which account for a much smaller proportion of the total speaking time than fundamental frequencies around the modal, may represent a characteristic inflection pattern in adductor spastic dysphonia. For example, the occurrence and extent of downward inflections may differ from those of the normal controls, and it could be that such time-varying phenomena, rather than the modal speaking fundamental frequency per se, are most important in these perceptions.

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ABNORMALITIES OF CILIA IN THE MIDDLE EAR IN CHRONIC OTITIS MEDIA

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We studied the fine structure of nasal and middle ear mucosa in 18 patients with chronic otitis media, comparing them with ten age-matched control patients. Electron microscopy revealed no single fundamental defect of cilia in the tissue samples; however, patients with chronic otitis media had a significantly higher incidence of abnormal cilia in the middle ear without correlating abnormalities of nasal cilia. These findings indicated that ciliary anomalies, including deletion of ciliary microtubules, presence of supernumerary tubules, and fusion of cilia, occur as a result of infection or inflammation. Such abnormalities would impair normal mucociliary clearance and exacerbate clinical complications.

KEY WORDS — cilia, epithelium, middle ear, otitis media.

INTRODUCTION

The mucosa of the upper respiratory tract is continuous with the eustachian tube and the middle ear, and is involved in the removal of exudates and contaminants.[1] In otitis media, mucociliary function can be disrupted by bacterial toxins,[2] by excessive mucous secretions, or by inflammatory processes.[3,4] Normal mucociliary function is believed to return after the inflammatory episode is resolved.[5,6] In chronic suppurative otitis media, mucociliary function may be either ineffective or totally absent.[7,8] The nature of this dysfunction is not as yet well understood or even studied. In other areas of the respiratory tract, in diseases such as bronchitis, ciliary dysfunction due to fusion of cilia and loss of microtubules and dynein components has been documented.[9,10] Some of these changes already have been noted in a few cases of chronic otitis media, as well as in serous otitis media.[11] However, similar changes may occur even in normal epithelium as a result of exposure to irritants in the atmosphere. The purpose of this study was to evaluate, by electron microscopy, the mucociliary epithelium in chronic otitis media and compare it with controls. Biopsied tissue from the middle ear also was compared to samples taken concurrently from nasal turbinates. The results show that, although ciliary defects occur to an appreciable extent in the normal epithelium of the middle ear, there is far more extensive damage in patients with chronic otitis media, which probably accounts for the impairment of mucociliary function.

MATERIALS AND METHODS

Samples of middle ear mucosa were obtained from the promontory in 18 adult patients (eight men, ten women) undergoing reparative surgery who presented with chronic suppurative otitis media and ten age-matched (age range, 30 to 50 years old) control patients (five men, five women) with no history of chronic otitis media who were undergoing tympanotomy for stapedectomy or ossiculoplasty at the Department of Otolaryngology, Toronto Western Hospital. Biopsies from the inferior nasal turbinates were taken concurrently from each patient. All tissue samples were collected with informed consent. Adequate tissue and structural preservation were obtained from the middle ear in nine patients with chronic otitis media and seven control subjects, and from the nasal turbinates in 14 patients with chronic otitis media and eight control patients. Any patient with an upper respiratory tract infection was excluded from the study.

Electron Microscopy. Biopsies of mucosa from the middle ear and from the nasal turbinates were fixed in 2% glutaraldehyde in 0.1 *M* sodium phosphate buffer with 1% tannic acid, rinsed in 0.1 *M* sodium phosphate buffer, postfixed in 1% osmium tetroxide in 0.1 *M* sodium phosphate buffer, dehydrated in graded ethanol solutions, and embedded in Epon-Araldite epoxy resin using flat-embedding molds to orient the epithelia.[9] Sections were cut approximately 1 μm thick on a Porter Blum ultra-

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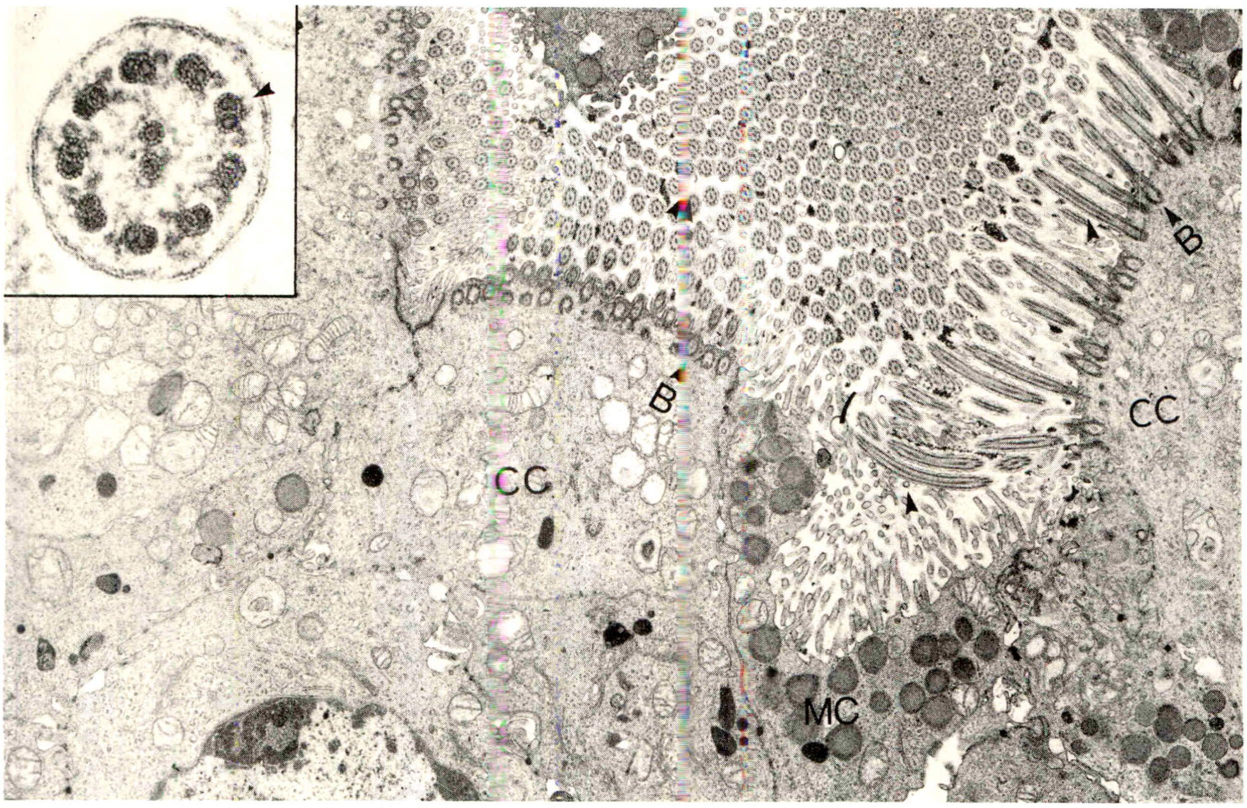

Fig 1. Longitudinal section of nasal mucosa from patient with chronic otitis media. Epithelium is composed of predominantly ciliated cells (CC) interspersed with mucus-secreting cells (MC). Cilia seen in longitudinal section (single arrowheads) and cross section (double arrowheads) arise from basal bodies (B) in apical cytoplasm of epithelial cells and project into airway lumen. Cilia in nasal mucosa from chronic otitis media and control groups are within normal range of appearance (original x7,600). Inset) Ultrastructural detail of nasal cilium cross section. Cilium is stained with tannic acid to demonstrate microtubular subunits and accessory proteins. Nine peripheral doublets (arrowhead) with hooklike dynein arms and two single central tubules characterize normal cilium (original x120,000).

microtome and examined by light microscopy. Ultrathin sections were prepared from selected areas, stained with uranyl acetate and lead citrate, and examined in a Philips EM 300 at 60 kV. From each biopsy ciliated cells were examined, in longitudinal sections to evaluate the number of cilia and the structure of the basal bodies and the ciliary axonemes, and in transverse sections of basal, middle, and apical regions. Ultrastructural features were recorded on electron micrographs at final magnifications of up to 150,000 diameters.

Evaluation and Enumeration of Ciliary Abnormalities. Ciliary ultrastructure was evaluated in transverse sections of mucosa from representative electron micrographs of the middle ear and the nasal turbinate. Normal cilia exhibited the typical arrangement of microtubules, with nine outer doublet tubules and two single central tubules. Dynein arms, inner and outer, are attached to the doublet tubules, and radial spokes connect the outer doublets with the central sheath that surrounds the singlet tubules. Normal cilia were enclosed within a continuous cell membrane. Ciliary abnormalities were classified into microtubular defects, including transposition of microtubules; supernumerary tubules; deletion of doublet microtubules; deletion of the central singlet microtubules; loss of dynein arms; and compound cilia, in which more than one ciliary axoneme was enclosed within a common cell membrane. The numbers of abnormal cilia were analyzed and expressed as a percentage of total cilia recorded on electron micrographs.

RESULTS

The ultrastructure of the cilia was similar from middle ear and nasal mucosal biopsy specimens. Fixation with glutaraldehyde and tannic acid clearly defined the ciliary membranes, microtubules, and accessory structures of the ciliary axoneme.

Nasal Mucosa Biopsy Specimens. The ultrastructural features of nasal mucosa from control patients and patients with chronic otitis media were essentially similar. The nasal epithelium was typically pseudostratified ciliated epithelium, interspersed with mucous secretory cells (Fig 1). The columnar ciliated and mucous epithelial cells showed extensive interdigitation of the lateral plasma membranes with intact apical junctional complexes. The structure and distribution of intracellular organelles, including mitochondria, Golgi complex, and endoplasmic reticulum, appeared normal. Mucous

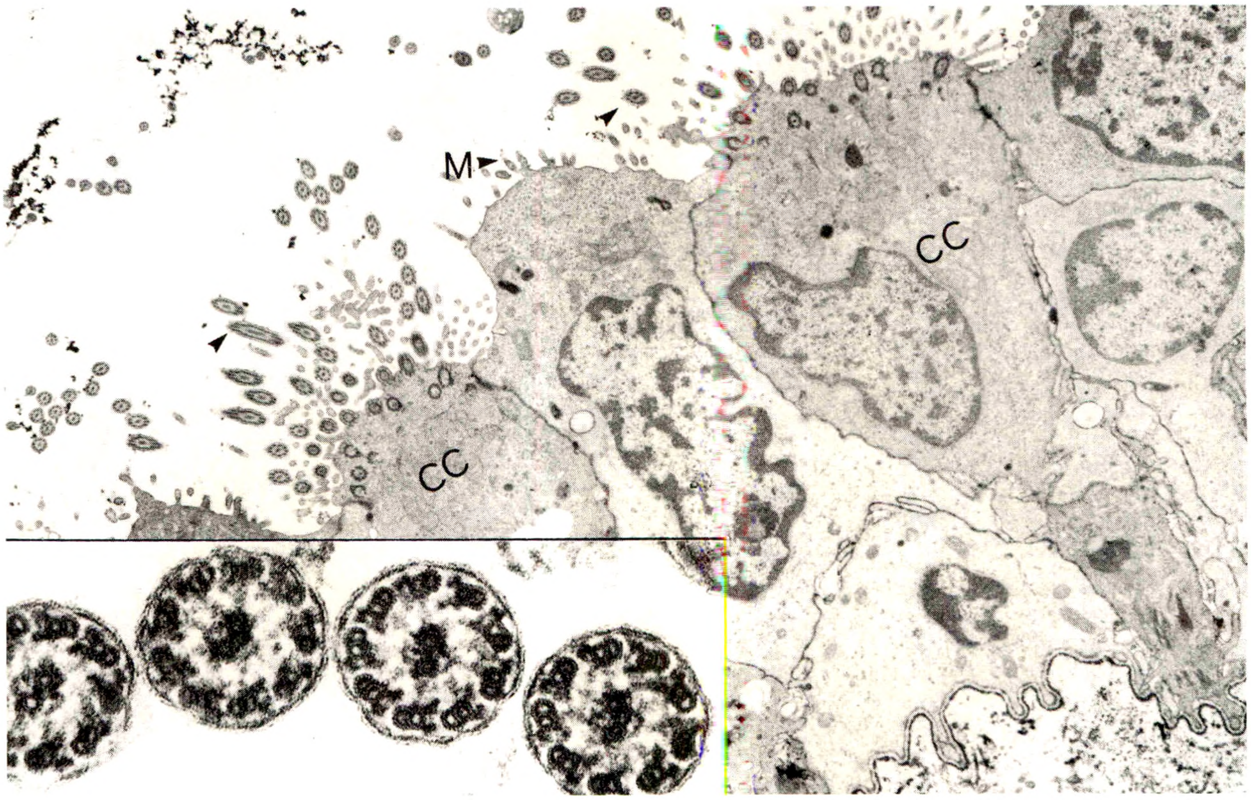

Fig 2. Longitudinal section of middle ear mucosa in chronic otitis media. Ciliated cells (CC) are sparse and interspersed with nonciliated cells that have short surface microvilli (M). Basement membrane is thickened by deposition of collagen fibrils deep to basal lamina (original x7,700). Inset) Detail of four cilia from middle ear in cross section. Arrangement of microtubules and parallel orientation of central pairs are indicative of normal structure and motility (original x92,000).

cell granules exhibited a fine internal fibrillar network. Long microvilli were seen on ciliated cells, in contrast to the stubby microvilli found on mucous cells. Few serous cell types were distinguished. Overall, there appeared to be a greater degree of epithelial cell degeneration and sloughing in biopsy specimens from patients with chronic otitis media. Moreover, in one case, basal cell hyperplasia was observed, and in another, the epithelium exhibited mucous cell hyperplasia. Again, in the samples from patients with chronic otitis media, the submucosa showed somewhat more edema. Some of the mucociliary and submucosal alterations may have been caused by handling artifacts introduced during the biopsy procedure. The changes indicated a generalized inflammatory condition that may have reflected upper respiratory tract infection or irritation.

Middle Ear Biopsy Specimens. In contrast to the epithelial lining of the nasal turbinates, the middle ear epithelium ranged from cuboidal to pseudostratified low columnar cells in control patients and patients with chronic otitis media (Fig 2). Most cells were either ciliated or nonciliated intermediate cell types, with short microvilli at their apical surfaces and few mucus-secreting cells. The ciliated cells of the middle ear had sparse numbers of cilia in comparison with those of the nasal epithelia. Biopsies from patients with chronic otitis media showed marked degenerative changes that included extensive edema in the submucosa, infiltration with inflammatory cells, wide intercellular spaces in the epithelium, extensive cell sloughing, cell blebbing, and apparent disruption or lack of basal lamina.

The incidence of ciliary abnormalities (Figs 3 and 4) was evaluated in biopsy specimens that included adequately preserved cilia, including middle ear epithelia from nine patients with chronic otitis media and seven control patients, and nasal epithelia from 14 patients with chronic otitis media and eight control patients (Table). The numbers of abnormal cilia were expressed as a percentage of the total number of cilia examined in transverse sections (for tubular anomalies) (Fig 3) or the total number of cilia in the biopsy specimen (compound cilia) (Fig 4). The incidence of abnormal cilia in the middle ear was 27.4% in patients with chronic otitis media compared to 13.0% in control patients. The incidences of compound cilia were 8.6% and 3.4% in patients with chronic otitis media and control patients, respectively. In nasal epithelia, the incidences of ciliary defects were approximately equal for patients with chronic otitis media (5.6%) and control patients (6.6%), and the percentages of compound cilia were 3.6% and 4.2% in patients with chronic otitis media and control patients, respectively. It appeared, therefore, that ciliary abnormalities occurred more commonly in the middle

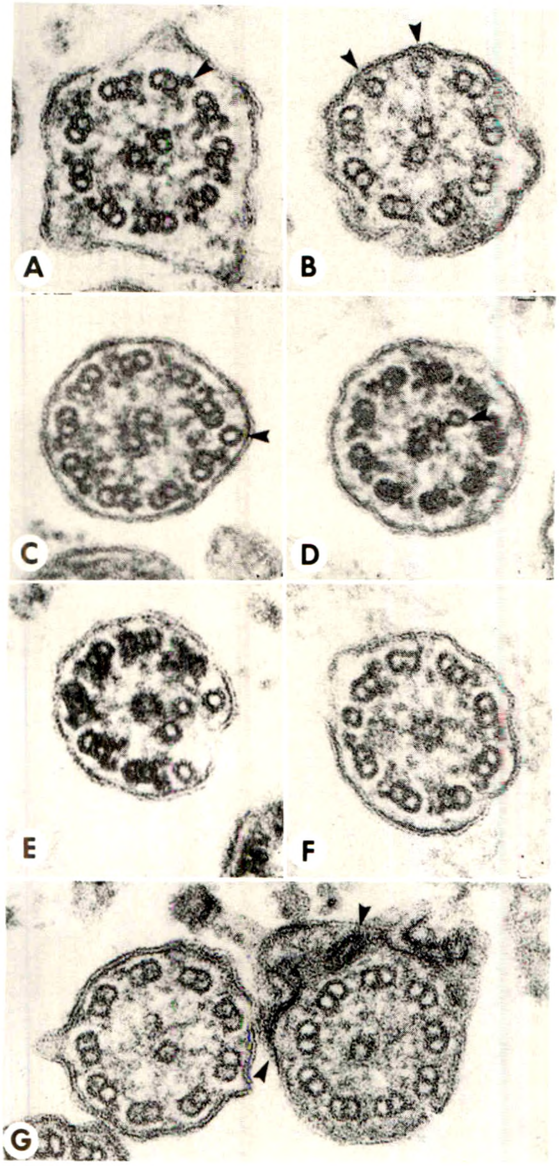

Fig 3. Transverse sections of cilia illustrating nonspecific ultrastructural changes in middle ear in chronic otitis media (original x110,000). A) Normal; nine outer doublets and two single central tubules (9 + 2 pattern); dynein arms (arrowhead) are attached to outer doublets; radial spokes interconnect outer tubules and central core. Cytoplasmic matrix is swollen, giving an irregular membrane surface. B) Apical region; doublet tubules do not extend to tip of cilium, and only singlet tubules are observed (arrowheads). Dynein arms are sparse in this region. C) Cilium with 9 + 2 pattern and supernumerary tubule (arrowhead) in peripheral cytoplasm. D) Cilium with supernumerary tubule (arrowhead) in central core. E) Cilium with abnormal complement and arrangement of microtubules. F) Cilium with deletion of central tubules. G) Two cilia, each with deletion of one central tubule. Abnormal membrane surface (arrowheads) reflects early changes that result in fusion of cilia.

ear biopsy specimens from patients with chronic otitis media. The abnormalities were nonspecific in nature, but were localized in the middle ear and were not accompanied by ciliary changes in nasal epithelial cells.

Among ciliary abnormalities in the middle ear, the loss of the central tubules occurred most frequently, followed by the presence of supernumerary microtubules, transposition of tubules, and loss of doublet microtubules (Fig 3). In control patients, loss of central tubules from cilia was uncommon, whereas deletion of tubules or supernumerary tubules occurred at a similar frequency. These changes were variable in nature and severity and considered to be secondary phenomena. No specific changes were observed consistently among cilia.

DISCUSSION

In recent years, hereditary defects have been identified in the nasal mucosa and lungs as causes of chronic respiratory disease. The clinical implications include chronic sinusitis, recurrent otitis, bronchitis, and bronchiectasis.[9,10] Because of the role of the mucociliary clearance system in the middle ear,[7,11,12] it is of particular interest to determine whether ciliary defects play a role in patients with chronic otitis media similar to those described in the middle ear in the immotile cilia syndrome.[13-15]

Chronic otitis media has been postulated to evolve from either previous acute episodes of otitis media, invasive osteitis, stasis of exudates, or eustachian tube inadequacy.[16,17] The role of pathogenic organisms in several forms of otitis media is well established,[18] although their contribution to its development is unclear. In general, recurrent and prolonged episodes of otitis media induce mucous cell hyperplasia or hypersecretion and may be complicated by additional tissue alterations such as edema, metaplasia of the epithelium, and inflammatory cell infiltration.[10,18,19] Many of these changes may arise as a result of eustachian tube dysfunction, perhaps because of ineffective mucociliary clearance.

Ultrastructural examination and quantitation of ciliary abnormalities in this study revealed that patients with chronic otitis media have significant alterations of normal epithelial function in the middle ear, even though cilia in the nasal mucosa appeared normal. Approximately twice as many cilia in the middle ear were defective in the patients with chronic otitis media as in control patients. The mechanisms responsible for ciliary anomalies are not known; however, loss of the central microtubules may correlate with autolysis of cilia because of endogenous activity of proteolytic enzymes. This type of defect has been reported to occur in bronchial mucociliary epithelium in patients with cystic fibrosis.[20] The deletion of tubules or occurrence of supernumerary tubules presumably reflected incomplete or defective ciliation during rapid regeneration of cells in previously damaged mucociliary epithelium.

Fused or compound cilia have been reported in limited numbers in normal subjects[9,10,21,22] and fre-

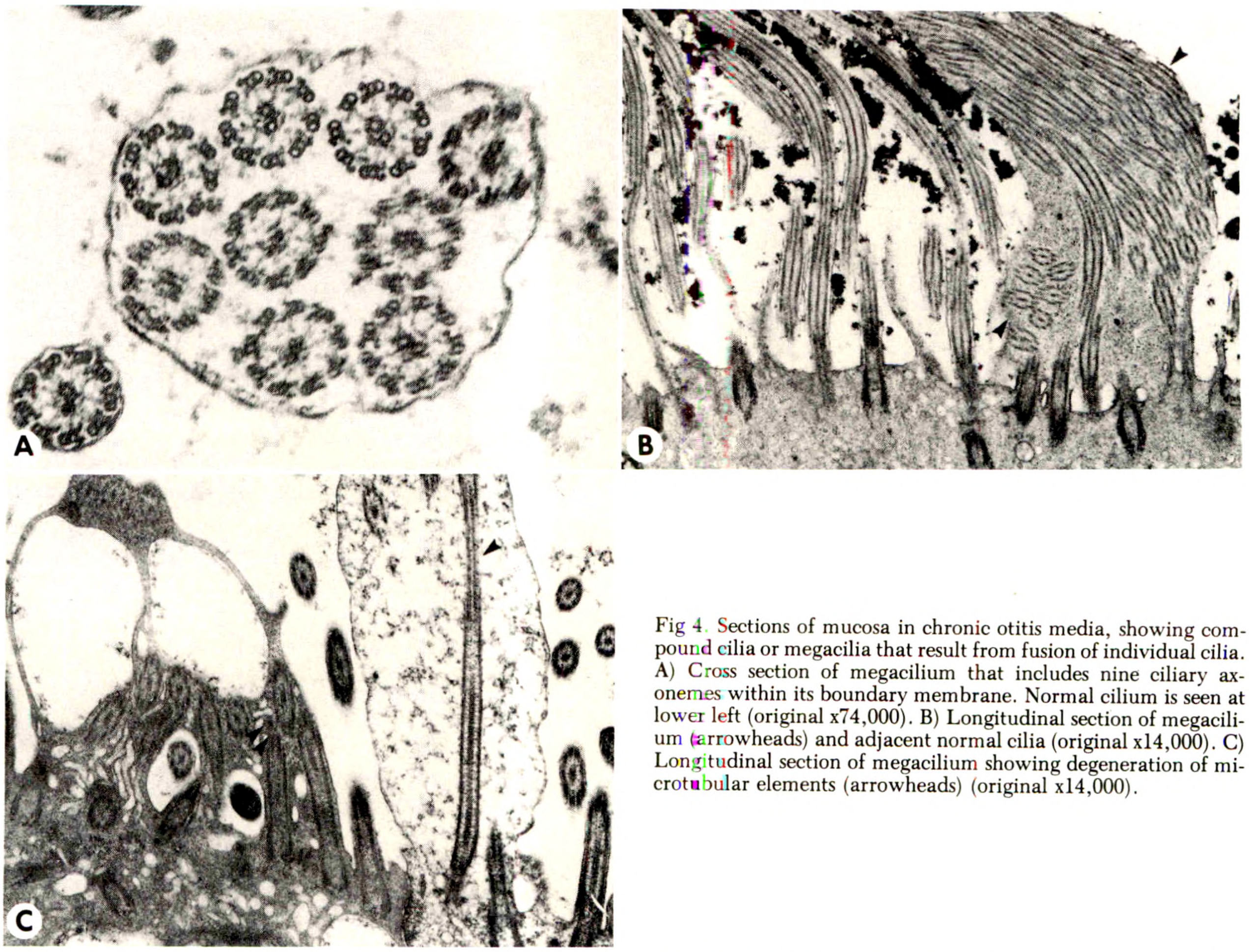

Fig 4. Sections of mucosa in chronic otitis media, showing compound cilia or megacilia that result from fusion of individual cilia. A) Cross section of megacilium that includes nine ciliary axonemes within its boundary membrane. Normal cilium is seen at lower left (original x74,000). B) Longitudinal section of megacilium (arrowheads) and adjacent normal cilia (original x14,000). C) Longitudinal section of megacilium showing degeneration of microtubular elements (arrowheads) (original x14,000).

quently in the middle ear of patients with cleft palate and serous otitis media.[12,13] Thus, fusion of cilia that may be attributed to local inflammatory conditions occurs more often in patients with otitis media than in control patients. The changes indicate that ciliary activity is compromised in patients with chronic otitis media, both from the loss of cilia and the increase in abnormal cilia. These changes are considered to impair normal mucociliary defense mechanisms.

Regardless of the pathogenesis of chronic otitis media, cytoprotection or repair of the mucosa is important to restore normal function. It is not known whether in chronic otitis media the mucociliary epithelium regenerates fully following treatment or surgical intervention. In rodents, after mechanical injury, regeneration of a completely functional mucociliary epithelium in the respiratory tract requires at least 1 week.[15,23] Newly derived ciliated cells appear within 60 hours and may originate from either mucous cells after a dedifferentiation process and/or from intermediate and basal cell progenitors.[24,25] The time frame for mucociliary regeneration in the human respiratory tract is not known, but is considered to be in the range of 7 to 10 days. Recently, ciliogenesis has been described in hamster tracheal epithelium in vitro in a serum-free, hormone-supplemented medium.[26] This process is dependent on vitamin A, since depletion of this factor rapidly leads to squamous metaplastic changes both in vivo and in vitro.[27] Thus, future therapeutic modalities

SUMMARY OF CILIARY ABNORMALITIES AND COMPOUND CILIA IN MIDDLE EAR AND NASAL TURBINATE

		% Abnormal Cilia*		% Compound Cilia†	
Source of Biopsy Tissue	*No. Subjects*	*Mean*	*Range*	*Mean*	*Range*
Patients with chronic otitis media					
Middle ear	9	27.4	0-36	8.6	0-36
Turbinate	14	5.6		3.6	
Control patients					
Middle ear	7	13.0		3.4	
Turbinate	8	6.6		4.2	

*Ciliary abnormalities include transposed tubules, loss of inner or outer dynein arm, supernumerary tubules, or deletion of peripheral doublet or central tubules.

†Percentage of compound cilia (≥ 2 ciliary axonemes within plasma membrane) based on all cilia recorded in electron micrographs.

might include, in addition to antibiotics and surgical management, supportive therapy with factors such as vitamin A that are obligatory for regeneration of a functional mucociliary epithelium.

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Ann Otol Rhinol Laryngol 97:1988

HUMAN LEUKOCYTE ANTIGEN-A, -B, -C TISSUE TYPES IN PATIENTS WITH MIDDLE EAR CHOLESTEATOMA

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Two series of consecutive, nonrelated patients with middle ear cholesteatoma verified by operation were tissue typed for human leukocyte antigens (HLAs) in order to demonstrate any associations. The first series (102 patients) showed only a possible increase of HLA-B8 and HLA-A2. Because HLA-B8 is one of the antigens most often involved in associations with organ-specific autoimmune diseases, and because of the close relationship between HLA-B8 and HLA-DR3, the second series (48 patients) was tissue typed for these two antigens. This second series showed a similar increase of HLA-B8/DR3, but the difference was not statistically significant.

KEY WORDS — cholesteatoma, tissue types.

INTRODUCTION

The cause of cholesteatoma in the middle ear is not clear, even though a tremendous amount of research has been performed in this area. Over the last century, the dominating theories of the genesis of cholesteatoma have been as follows. The emigration theory was proposed in 1888 by Habermann,[1] who suggested that squamous epithelium from the ear canal grew into the middle ear through a defect in the tympanic membrane. Bezold[2] suggested the retraction pocket theory in 1891, with reduced function of the eustachian tube and consequently low middle ear pressure as the provoking factor. The metaplasia theory, first mentioned by Ulrich[3] in 1917, suggests that the mucous membrane of the middle ear is transformed to keratinizing squamous epithelium. Lange[4] suggested in 1925, after histologic investigation, that papillary proliferation takes place from epidermal cells in the pars flaccida of the eardrum. None of these theories has been able to give a full description of the cause of middle ear cholesteatoma.

Human leukocyte antigen (HLA) tissue typing was developed in connection with kidney transplantation. The antigens since have been studied on a considerable number of diseases, and it has been shown that some diseases are associated with certain antigens. This indicates that in the HLA system there are genes that confer susceptibility to particular diseases.

The most notable example is the association between B27 and ankylosing spondylitis, in which the antigen is found in 80% to 100% of patient groups, compared with 4% to 13% in control populations[5]; but the association is far less conspicuous in other diseases (eg, diabetes, multiple sclerosis). The latest news from this particular field is the 1986 study of Xenellis et al,[6] who found that 75% of Meniere's disease patients had the HLA-Cw7 antigen. Compared with the control group, there was a highly significant difference, even after correction was made for the numbers of antigens tested ($p = .035$).

As a measure of association, it has become customary to use the relative risk, which is the ratio between the risk of contracting the disease among persons with the antigen and that among persons without the antigen. Disease associations have, of course, great theoretic interest, as they indicate both genetic and immunologic components of the disease; but in some cases they are also of diagnostic and prognostic value.

A positive association between a tissue antigen and middle ear cholesteatoma would have great importance. Patients with cholesteatoma require costly treatment, and a prophylactic effort by tissue typing could mean a possibility of intervention in these patients before damage develops in the middle ear and inner ear. The purpose of the present study was to investigate the HLA antigenic profile in patients with middle ear cholesteatoma and, if possible, to demonstrate an association.

MATERIAL AND METHODS

We studied two series of consecutive, nonrelated patients. The first series consisted of 102 patients, and the second series of 48 patients. The criterion for inclusion was an operatively verified cholesteatoma in a retraction pocket extending from the pars flaccida of the eardrum. Cholesteatoma from the pars tensa of the eardrum was not included. No primary cholesteatoma was found in these groups of patients. Children less than 10 years of age were not studied because of ethical considerations concerning blood samples. Patients more than 55 years old

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TABLE 1. HLA-A, -B, -C ANTIGEN DISTRIBUTION

Antigen	*Patients** *No.*	*%*	*Controls†* *No.*	*%*	*p Value (%)*	*Relative Risk*
A1	30	29	924	32	48.00	0.88
A2	67	66	1,524	53	1.70	1.67
A3	29	28	847	30	72.00	0.96
A9	12	12	497	17	11.00	0.66
A10	13	13	254	9	24.00	1.55
A11	9	9	320	11	37.00	0.81
Aw19	15	16	496	19	41.00	0.84
A28	10	10	241	8	76.00	1.23
B5	14	14	299	10	38.00	1.40
B7	26	25	833	29	36.00	0.84
B8	35	34	648	23	0.85	1.80
B12	25	25	746	26	63.00	0.93
B13	2	2	116	4	44.00	0.59
B14	2	2	90	3	76.00	0.76
B15	21	21	542	19	77.00	1.12
Bw16	5	5	158	6	59.00	0.94
B17	6	6	205	7	49.00	0.87
B18	7	7	217	8	64.00	0.95
Bw21	4	4	72	3	54.00	1.75
Bw22	2	2	101	4	60.00	0.68
B27	9	15	254	13	84.00	1.04
Bw35	15	15	370	13	78.00	1.16
B37	3	3	78	3	87.00	1.03
B40	12	12	534	19	5.80	0.60
Bw41	3	3	34	1	39.00	2.38
Cw1	7	7	139	5	49.00	1.53
Cw2	9	9	279	10	61.00	0.93
Cw3	29	28	820	35	15.00	0.75
Cw4	17	17	338	14	63.00	1.21

*102 patients with cholesteatoma.

†Approximately 3,000 blood donors.

were also excluded to avoid changes due to age. The first series consisted of 64 men and 38 women. The age median for the men was 35 years (range, 12 to 55) and for the women 34 years (range, 11 to 48). The second series was equivalent to the first in age and sex.

Tissue typing was performed in the Department of Clinical Immunology at the University Hospital of Aarhus, using a standard lymphocytotoxic microtechnique with identification of antigens on living, isolated lymphocytes.[7] In the first series, eight HLA-A, 17 HLA-B, and four HLA-C antigens were determined. In the second series, only HLA-B8 and HLA-DR3 were determined. As controls, a group of approximately 3,000 blood donors were chosen randomly from a cohort of nonselected, unpaid, healthy volunteers of both sexes between the ages of 18 and 60 years.

The test groups and the control groups were comparable in age, and so far there have not been shown any HLA associations to age and sex. Furthermore, with an incidence of eight persons per 100,000 with cholesteatoma in Denmark,[8] we found it most unlikely that any cholesteatomas should be represented in the control group. For each antigen, the frequencies among the patients and the controls were compared using a χ^2 test or, if appropriate, Fisher's exact test. Tests for ABO blood grouping were performed in the first series, using a simple agglutination test, testing both for antigen and antibody.

TABLE 2. ABO PHENOTYPE DIAGNOSIS

Blood Group	*Patients** *(No.)*	*Controls†* *(%)*	*p Value* *(%)*
O	43	42	87
A	47	44	66
B	10	10	85
AB	2	4	66

* 102 patients with cholesteatoma.

† Approximately 3,000 blood donors.

RESULTS

Table 1 shows the comparison of antigen frequencies in the two groups with the p values of significance and the relative risk of disease. One antigen, HLA-B8, is remarkable, with frequencies of 34% and 23% in patients and controls, respectively, and a p value of .0085. This corresponds to a relative risk of 1.8, which means that a person with HLA-B8 is 1.8 times more likely to develop cholesteatoma than a person without this antigen. We also found HLA-A2 with a p value that seems highly significant, but is actually not. The reason is that a great number of uncritical comparisons have been performed with an ensuing increase in the risk of a type 1 error.[9] To counter this it has become customary to divide the 2 x α values with the number of comparisons performed.[10] This means that the critical p value for significance becomes .05/29 or .0017. This means that the significances for B8 and A2 disappear.

Human leukocyte antigen Bw41 had a relative risk of 2.38. This value is without any significance compared to the high p value of .39. The relative risk is high, because of the low frequency of the antigen.

The distribution of ABO blood groups from the first series was very similar in patients and controls (Table 2). Table 3 shows the results from the second series, in which 48 patients were tested for two HLAs. The expected high frequency of DR3 compared to B8 was not found. The two antigens had similar p values and relative risks. A possible association was therefore insignificant. Despite this, it is notable that if the number of patients is extrapolated from 48 to 102, the χ^2 value increases to 2.23 x 102/48 and equals 4.74. This would give a p value

TABLE 3. DISTRIBUTION OF HLA-B8 ANTIGEN AND HLA-DR3 ANTIGEN

Antigen	*Patients** *No.*	*%*	*Controls†* *No.*	*%*	*χ^2 Value*	*p Value*	*Relative Risk*
B8	15	31	647	23	2.23	0.14	1.58
DR3	15	31	45	22	1.85	0.17	1.60

*48 patients with cholesteatoma.

†Approximately 3,000 blood donors.

of less than .05. This, of course, would demand the same frequencies of antigens for the extrapolated number of patients.

DISCUSSION

In the present investigation we found no significant association between cholesteatoma and the HLA system. The results obtained in the first series made it reasonable to expect stronger associations between HLA-DR3 antigen and cholesteatoma than were found for antigen HLA-B8.[9]

This antigen was not determined in the first series. In the second series (Table 3) we tested only the two interesting antigens, and it is therefore not necessary to correct the p values for type 1 errors. Nevertheless, the p values do not reach significance. It should be noted that even if the association were at a significant level, the size of relative risk would have to be considerably larger to be of clinical importance.

Results of the blood type investigation showed no differences in the distribution of antigens between the group of patients with cholesteatoma and a control group (Table 2). Similar results were found by Mortensen et al.[11]

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THIRD INTERNATIONAL CONFERENCE ON CHOLESTEATOMA AND MASTOID SURGERY

The Third International Conference on Cholesteatoma and Mastoid Surgery will be held June 5-9, 1988, in Copenhagen, Denmark. For further information, contact Cholesteatoma Conference Secretariate, ENT Department, Gentofte Hospital, DK-2900 Hellerup, Denmark.

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COMPUTERIZED DATA BANK SYSTEM FOR TEMPORAL BONE HISTOPATHOLOGY

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A computerized data bank system to store and analyze temporal bone histopathologic data is described. This system uses the University of Pittsburgh's Digital Equipment Corporation System 10 computer and the System 1022 data base management software. Data on histology cases are divided into five files: general information, otologic information, summary, histopathologic information about the external ear and middle ear, and histopathologic information about the inner ear. Eleven general terms are used to describe pathologic findings, surgery, postmortem degeneration, and artifacts. In addition, provision is made for the inclusion of more precise qualitative information to be entered as text.

KEY WORDS — temporal bone data bank, temporal bone histopathology.

INTRODUCTION

Computerized data banks are used widely in the medical field in both clinical and research settings because they permit the rapid management and analysis of large amounts of data. We currently have more than 1,000 temporal bones in our laboratory. Previously, data on each case were entered by hand on temporal bone worksheets, and histopathologic reports were kept in file folders. Thus, when we wished to review a case demonstrating a particular disease or condition, or disorder in a particular site, each case had to be reviewed. In order to eliminate these time-consuming searches, we developed a computer-based system for the storage, retrieval, and analysis of data pertaining to temporal bones. Examples of computer-generated histopathologic reports and the structural details of the data files are available from the corresponding author (I.S.) upon request. The development of this system proceeded using the University of Pittsburgh's large time-shared computer system, which has the System 1022 Data Base Management System[1,2] available to all users.

SYSTEM

The main computer at the University Computer Center is a Digital Equipment Corporation (DEC) System 10, running a modified version of the TOPS 10 Operating System. Users log into the system at remote job entry sites having public terminals or through 300- and 1,200-baud dial-up lines. Our data base was developed using a DEC VT100 CRT terminal and a Xerox 1730 terminal for hard copy output. Both of these are connected to the computer system via a 1,200-baud modem.

STRUCTURE AND DESCRIPTION OF DATA SETS

Data originally stored on the temporal bone worksheet (TBW) on each temporal bone specimen were cataloged in five subgroups in the five computer files (TBWs 11, 22, 33, 44, and 55). The exact format of these files is available from the author. A brief description of each file is given below. Capitalized expressions in parentheses indicate the attribute name used in the file, eg, TBID is the temporal bone identification number.

TBW 11 is a file for general information, including the temporal bone identification number (TBID), temporal bone group identification and its own number, side (right or left), name of patient, age, sex, race, general diagnosis, date of death, name of hospital, autopsy number, postmortem hour, name of person who removed the specimen, and other information (eg, name of otologist who treated the patient). In order to use files systematically, each temporal bone is assigned a unique TBID that is used on all TBW files. Five attributes (years, months, weeks, days, and gestational weeks) are used to record the ages of specimens, adult (years only) to fetuses (gestational weeks).

TBW 22 is a file for otologic information, including otologic diagnosis, hearing loss (severity, type, and course), balance disturbance (severity, type, and course), and facial nerve dysfunction (severity, type, and course). There is also an attribute allotted to record the results of tests (TEST).

TBW 33 is a file for summarizing the histopathologic findings in each case, and includes information about artifacts and postmortem degeneration, as well as the name of the otopathologist who evalu-

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ated the case. Eleven general terms are used for data entry: six indicate definite pathologic conditions including malformation (MAL), inflammation (INF), degeneration (DEG), circulatory dysfunction (CD), trauma, and tumor; the others indicate other pathologic findings (OTH), normal findings, surgical procedures (SRG), postmortem degeneration (PMD), and artifact. These 11 general terms are also used as a starting point in the more detailed descriptions that are contained in the following two files, TBW 44 and TBW 55. The more detailed files also have room to record qualitative descriptions that explain a type of disease more precisely.

TBW 44 records the detailed results of studying the external and middle ear histopathology. Each anatomic structure in the external and middle ears is assigned an attribute, as decided by evaluation of the worksheet already in use to record these data.

The user enters a word description into 18 attribute fields representing the anatomic terms for structures of the external ear, the middle ear, and associated regions. To begin with, this description uses one or more of the 11 general terms described above in TBW 33. Next, the severity and/or location of the disease also is stated. Thus, "INC — MAL FETAL FORM" indicates that the incus is malformed, specifically that it is in the fetal form.

TBW 55 is a file for recording histopathologic findings in the inner ear. Those attributes are assigned to anatomic structures in this part of the inner ear, with the anatomic structures to be evaluated also being chosen to correspond to those on the worksheet already in use.

The same procedure that is used for TBW 44 is used for data entry into this file. One or more of the 11 general terms is entered, and that is followed by a more precise description that might include the severity and/or the location of the disease. For example, "COCHLEA — MAL 1 & ½ TURN" means malformation in the cochlea — it has only one and a half turns. The term "CN — DEG LOSS BT, MT" means the cochlear nerve (CN) has degenerated (DEG), resulting in cochlear nerve loss in the basal turn (BT) and middle turn (MT).

For routine study of temporal bones, these files have been found to be adequate to record the most important temporal bone histopathologic findings. This system of subgroups is useful not only for organizing information, but also for increasing the efficiency of data handling, since each separate group can be manipulated as a unit.

COMPUTER ENTRY OF DATA

The data collection forms are in a question-response format. Each source form is treated as a set of questions, and each question requires a single response from the user. The type of response is classified as a real number, integer, date, or text.

In order to use file TBW 11, for example, the user would respond to each of the prompts (in capital letters) below with the information following the colon.

TBID: Enter a six-digit temporal bone identification number. This number consists of the group, the case number, and the side designation (right or left). The first digit indicates the group, the second to fifth digits indicate the case number, and the last digit indicates the side of the ear: 0 for right and 1 for left.

GROUP: Temporal bones are assigned to one of three groups (P, H, or B), according to their source.

NUMBER: Each temporal bone in a group is assigned the next consecutive number in that group.

SIDE: Enter the side of the ear. R indicates right ear and L indicates left ear.

NAME: Enter patient's last name, (middle name), first name.

AGE-YEAR: Enter age in years using three integers for adults and children more than 2 years old.

AGE-MONTH: Enter age in months using two integers for infants and children less than 2 years old.

AGE-WEEK: Enter age in weeks using two integers for infants less than 3 months old.

AGE-DAY: Enter age in days using two integers for newborns less than 3 weeks old.

FETUS-WEEK: Enter age in weeks' gestation using two integers for fetuses and premature babies.

SEX: Enter M for male or F for female.

RACE: Enter W for white, B for black, or O for others.

GDX: Enter general diagnosis. More than one diagnosis can be entered in text. No coding system is used.

DATE OF DEATH: Enter as month-day-year in date.

HOSPITAL: Enter hospital name.

AUTOPSY NUMBER: Enter the autopsy number.

POSTMORTEM HOUR: Enter postmortem hour using two integers.

REMOVED BY: Enter the name of the person who removed the temporal bone.

OTHER NUMBER: Enter additional numbers used to identify specimens cut vertically, E-45 for a specimen cut vertically to include the eustachian tube, and SP-3 for a specimen cut vertically that includes the eustachian tube and soft palate.

OTHER INFORMATION: Enter any other pertinent information, eg, name of physician who treated the patient from whom temporal bone was obtained.

DATA BANK USE

Three examples that illustrate data bank use are case reports, inspection of cases using the data base MAP function for cross-indexing, and a statistical analysis of dimensional data taken from eustachian tube samples.

Example of Case Report. The standard temporal bone histopathologic report is in four sections: personal information, otologic information, a summary of the detailed findings, and the detailed findings themselves. The primary purpose of this report is to make the information entered into the temporal bone bank available to the researcher in readable, understandable form.

Example of Cross-Reference Function. As an example, the file is searched for the occurrence of trisomy in the general diagnosis (GDX) category. Next, the 11 occurrences of this finding are cross-referenced to file TBW 44 so that detailed information concerning the disease of the middle ear, for example, can be printed out.

Files are searched for the occurrence of the diagnosis of trisomy, and these files are sorted in order and then printed out. Next, the data from another file are cross-referenced using the MAP command. (The System 1022 MAP command locates records in one data set that are related to records in another data set.) Then the information concerning anomalies of the ossicle chain is printed out in the same order. Although this example of cross-referencing is very simple, more complex cases can be constructed using logical mathematic operations. For example, it would have been possible to have printed out only the findings of those patients who were above a certain age, as an additional condition to the cross-referencing.

Example of Statistical Function. Our data base system and the modular structure of our files make it very easy to use the generalized system for specialized applications. For example, one could use two additional files that contain qualitative and quantitative data about the eustachian tube from a specific subpopulation of the temporal bone samples. Once the data have been entered, generating the reports is a two-step process. First, the researcher has the program perform statistical functions upon certain selective measures, in this case the area, length, and width of the lumen of the eustachian tube. The mean and standard deviation of these measures can be calculated. Next, this information is printed out in the report format.

DISCUSSION

The examples discussed above were deliberately simple ones. It is possible to write more complex reports and use more complex cross-reference functions. The MAP and statistical functions could be used in a stepwise procedure as well. For example, the researcher could examine the mean and standard deviations of all patients having one general diagnosis and could compare those data with the measurements taken from a group of normal subjects to determine whether there was an anatomic correlate with the disease in question. Alternatively, the researcher could begin the search by determining which temporal bone samples had dimensions that were one or more standard deviations larger than the normal limits. By the MAP command, the diagnoses of these persons now could be listed and examined for interesting patterns by the researcher.

The researcher is thus able to make many kinds of comparisons between different aspects of the data in a time-efficient manner. The price for this is that the data must be entered into the data pool and that the researcher must be familiar with the capabilities of the data base management system. This procedure has been implemented for many other medical data bases around the world, which is testimony that the information gained is worth the price to gain it.

CONCLUSIONS

1. The temporal bone data bank is advantageous to the researcher because it provides a means of accurately keeping track of temporal bone histology data that can be recorded by trained secretarial personnel, thus allowing the researcher more time to do the more specialized functions for which he or she has been trained.
2. The MAP function available in the data base management system enhances the capability of the temporal bone pathologist because it allows for the listing of a second attribute based upon the occurrence of a first specified attribute in the data file. Using file cards or other manual methods can be very time-consuming, compared to the way a data base management system can provide the same information.
3. The statistical functions available in the data base management system allow researchers to make many preliminary comparisons of their data in a way to test quickly a number of initial hypotheses. This process can be very important in the initial direction of a temporal bone study.
4. Because of the modular arrangement of the temporal bone data base subcategories, it is extremely easy to add on extra files for specific research studies. The keying using TBIDs now will allow the separate modular components of the data base to be tied together via data base MAP functions, and thus several diverse attributes can be

compared.

5. Finally, the format and structure of the temporal bone data base can serve as a standard for other investigators, who can use it directly on a 1022 data base management system, or use similar concepts for other systems.

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AMERICAN AUDITORY SOCIETY

The 15th annual meeting of the American Auditory Society will be held in Boston on Thursday, November 17, 1988. The meeting is scheduled in conjunction with the annual meeting of the American Speech-Language-Hearing Association. For further information, contact Frank E. Musiek, PhD, Program Chairman, Dartmouth-Hitchcock Medical Center, 2 Maynard Street, Hanover, NH 03756.

Ann Otol Rhinol Laryngol 97:1988

STUDY OF TOYNBEE PHENOMENON BY COMBINED INTRANASOPHARYNGEAL AND TYMPANOMETRIC MEASUREMENTS

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The Toynbee maneuver, swallowing when the nose is obstructed, leads in most cases to pressure changes in one or both middle ears, resulting in a sensation of fullness. Since first described, many varying and contradictory comments have been reported in the literature concerning the type and amount of pressure changes both in the nasopharynx and in the middle ear. In our study, the pressure changes were determined by catheters placed into the nasopharynx and repeated tympanometric measurements. New information concerning the rapid pressure variations in the nasopharynx and middle ear during deglutition with an obstructed nose was obtained. Typical individual nasopharyngeal pressure change patterns were recorded, ranging from a maximal positive pressure of + 450 to a negative pressure as low as − 320 mm H_2O.

KEY WORDS — eustachian tube, middle ear pressure, nasal pressure equalization tube, nasopharyngeal pressure, Toynbee maneuver, Toynbee phenomenon.

INTRODUCTION

In 1853, Toynbee[1] observed that a swallowing movement performed at the same time the nose is obstructed, known as the Toynbee maneuver, causes a feeling of increased pressure in the ears. Toynbee proposed that air was passed into the middle ear during the first deglutitory movement, causing a pressure rise in the middle ear. The effect of the pressure changes within the nasopharynx on the eustachian tube and the middle ear has been defined as the Toynbee phenomenon[2-4] and often results in a sensation of fullness in one or both ears.

In 1861, Politzer[5] suggested that Toynbee's theory of the effect of the maneuver on the middle ear pressure was incorrect. Using an ear manometer he found that the maneuver caused negative pressure in the middle ear. Four years later Politzer[6] modified his views. At the beginning of the maneuver he recorded a slight pressure rise in the middle ear, which was immediately followed by a pronounced pressure dip, persisting after the end of the maneuver. Politzer found that the pressure rise was 5 to 10 mm H_2O, replaced by a negative pressure of 60 to 120 mm H_2O. In 1951 Perlman[7] recorded negative pressures in the nasopharynx as low as 100 mm H_2O at the end of the maneuver.

The pressure changes during the Toynbee maneuver are important from a clinical point of view, as the maneuver is considered a valuable method for evaluating tubal function. The patient is asked to pinch his nose, thus closing his nostrils, and to swallow. At the same time the examiner observes the movement of the tympanic membrane.

In 1942, Zöllner[8] and, in 1957, Thomsen[9] found that in nearly 30% of the normal population who do not present signs of impaired tubal function, no movement is seen, thus false results may be obtained. In 1963 Ingelstedt and Örtegren[10] demonstrated three types of nasopharyngeal pressure complexes: negative, positive, and biphasic. The pressure gradients ranged from + 140 to −280 mm H_2O. They concluded that the degree of middle ear ventilation is entirely dependent on the amount and type of the pressure changes actually taking place in the nasopharynx during the tubal opening period. In 1971 Elner et al[11] found that in normal subjects the Toynbee maneuver resulted in negative middle ear pressure in 64%, alternately positive and negative pressure in 24%, and positive pressure in 12%.

In 1976 Andreasson and Ivarson[12] found the pressure waves in the nasopharynx were biphasic or polyphasic in 95% and negative in 5% of patients. The positive nasopharyngeal pressure varied from 10 to 100 mm H_2O and the negative from −10 to −340 mm H_2O. In 1973 Lamp[13] reported his observations in a large series of patients performing the Toynbee maneuver whom he categorized in three types according to the eardrum movement: 1) biphasic — first in, then out; 2) biphasic — first out, then in; and 3) a monophasic type of inward movement. In many others no perceptible motion was noted. In 1984 Jörgensen and Holmquist[14] found that after performing the Toynbee maneuver, 2% of normal individuals without obvious middle ear disease developed positive middle ear pressure, while 56% of the patients with middle ear disease developed positive middle ear pressure. They suggest that the positive pressure created in the nasopharynx when performing the Toynbee maneuver is a factor in middle ear disease.

Surprisingly, there are many different and often

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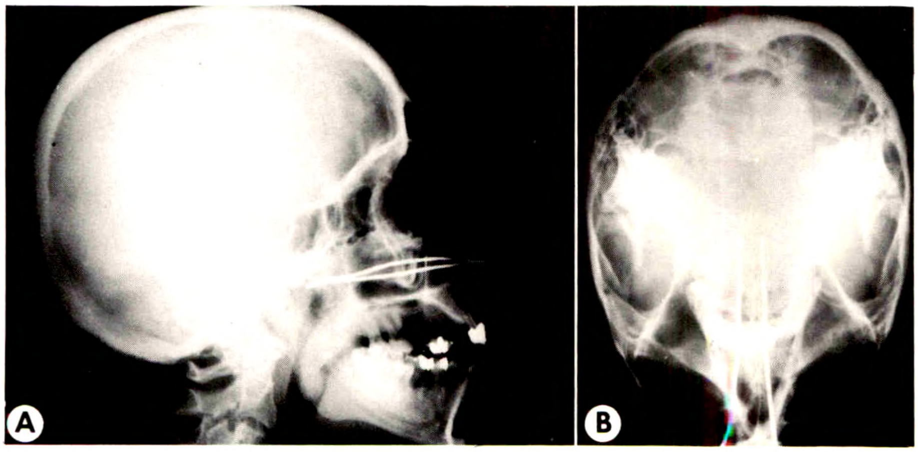

Fig 1. Radiopaque nasal catheters inserted through nasal cavity to posterior nasopharyngeal wall. A) Lateral view, B) basal view.

contradictory opinions and findings in the literature concerning the pressure changes in the nasopharynx and in consequence in the middle ear. According to Sade[15] and Bluestone et al[3,4] the profile of an initial positive phase followed by a negative phase always develops in the nasopharynx when swallowing at the same time that the nose is obstructed. Bluestone et al[4] also suggest that decreased effective nasopharyngeal volume by adenoids may increase the positive and negative nasopharyngeal pressures. Thus, 133 years after Toynbee's observation of the phenomenon named after him, the pressure gradients in the nasopharynx and in the middle ear during swallowing are yet to be clearly defined.

In all previous investigations, the pressure variations in the nasopharynx were recorded through nosepieces placed in the nostrils. Nasal airway resistance that varied among individuals[16-18] and the distensibility of the nasal cavity were not taken into consideration. These factors can completely alter the results of the measurements and thus be misleading. Our purpose was to analyze and clarify the phases of the Toynbee phenomenon. In the present study the pressure changes were measured precisely, directly from the nasopharyngeal cavity, and compared to measurements taken from the nostrils. Immediately after these measurements were taken, repeated tympanometric examinations were performed.

MATERIALS AND METHODS

In our study 37 patients who have undergone nasal septal surgery were assessed. Bilateral anterior nasal packing was inserted in all patients. Their ages ranged from 17 to 73 years with a mean age of 41 years. The group consisted of 28 men and nine women. All the patients had clinically normal velopharyngeal function and demonstrated good closure of the nasopharynx. One of them (patient 4) presented sclerotic eardrums with two retraction pockets on the left.

In order to measure the pressure developing in

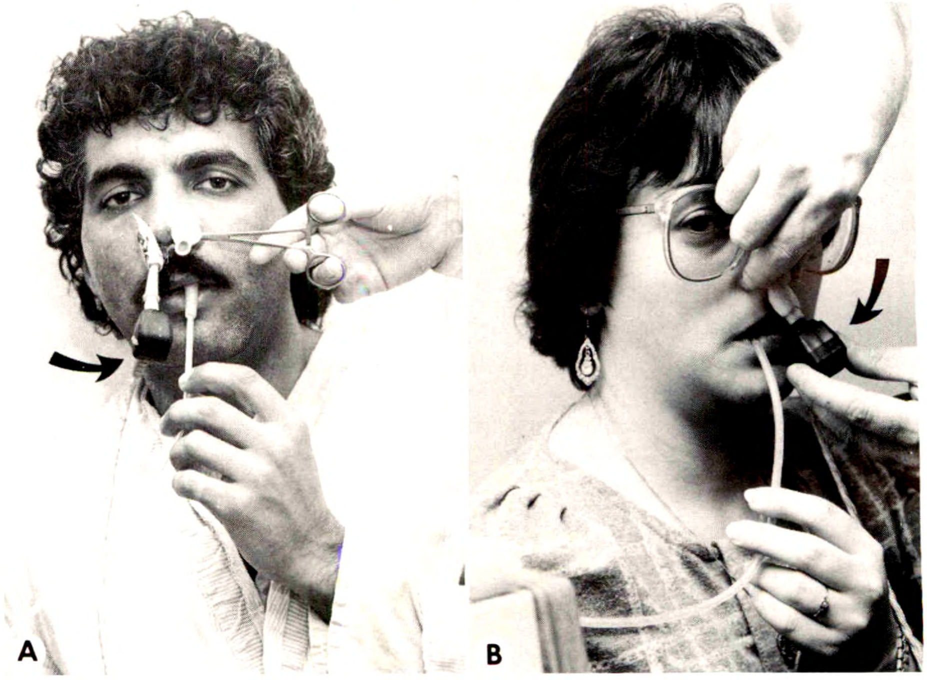

Fig 2. Manometric measurement of pressure changes in nasopharynx. A) Transducer is applied to one catheter (arrow); second catheter is clamped. Patient is swallowing water through elastic tube. B) Probe is applied to one nostril while nose is occluded between fingers of examiner.

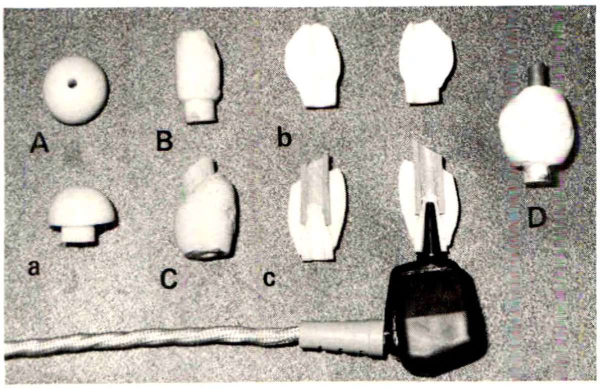

Fig 3. Various forms of nosepieces. A) Ear tip (No. 20) of middle ear analyzer and side view (a); B) ear tip encased in molded polymer of organic silicon and cut sections (b); C,D) ear tips with obliquely cut rubber tubes affixed to them encased by molded polymer of organic silicon. External contour is ellipsoid and oblique. c — cut section of ear tip C.

the nasopharynx, we inserted No. 16 Nelaton catheters between the layers of the nasal pack. The tubes were obliquely cut and their length adjusted proportionally, after measuring the distance from the nasal vestibulum to the posterior nasopharyngeal wall (Fig 1). A Grason-Stadler 1723 middle ear analyzer was used to obtain tympanometric patterns and recordings of pressure gradients within the nasopharynx. The analyzer used for testing eustachian tube function in patients with perforated eardrums is transformed to a pressure transducer recorder when the manual pressure knob is set to zero. In the recordings of pressure variations, the horizontal axis represents time (5 mm/s), and the vertical axis represents pressure (7.5 mm/100 mm H_2O). Positive pressure is recorded as upward curves and negative pressure as downward curves.

Before actual measurements were taken, the calibration of the system was tested by a water manometer within pressure ranges of +450 to −400 mm H_2O. The following measurements were taken in each patient: 1) tympanometry, 2) manometric determination of pressure changes within the nasopharynx during swallowing of water, and during empty (dry) deglutition (the probe of the transducer was securely applied to one catheter while the second catheter was clamped [Fig 2A]), and 3) repeated tympanometric measurements after multiple deglutitions of water with closed catheters, one by the transducer, and the second by a clamp. In ten randomly selected patients we also measured preoperative manometric recordings of pressure gradients that developed within the nasopharynx when the probe was applied to one nostril while the nose was occluded between the fingers of the examiner (Fig 2B).

The following measurement devices were used: 1) ear tips (No. 20) of the middle ear analyzer (Fig 3A), which replaced the nasal olives previously used; 2) various forms of nosepieces developed to achieve the best anatomically suitable form in order to reduce the nasal airway resistance. The nosepieces were shaped so as to eliminate the flow-limiting segments or valve effect.[19-23] Converted ear tips of the analyzer were used as nosepieces. An obliquely cut rubber tube was affixed to a polymer-covered ear tip (Fig 3C,D); 3) further measurements were taken after spraying the nasal mucosa with a 2% solution of ephedrin.[22-25]

The recordings were made while the patient, in a sitting position and on command, swallowed "dry" or water, which was drunk through an elastic tube to prevent unnecessary head movements. The transducer was applied to the funnel connector of the catheter (Fig 2A), or using the nosepiece, was applied to one nostril. The patency of the intranasal catheters was assured before each measurement.

RESULTS

Manometric measurements through the catheters during deglutition revealed pressure gradients within the nasopharynx ranging from as high as +450 mm H_2O (Figs 4 and 5, patient 1), to as low as −320 mm H_2O (Figs 4 and 5, patient 37). The mean positive pressure was 180 mm H_2O with an SD of 97.

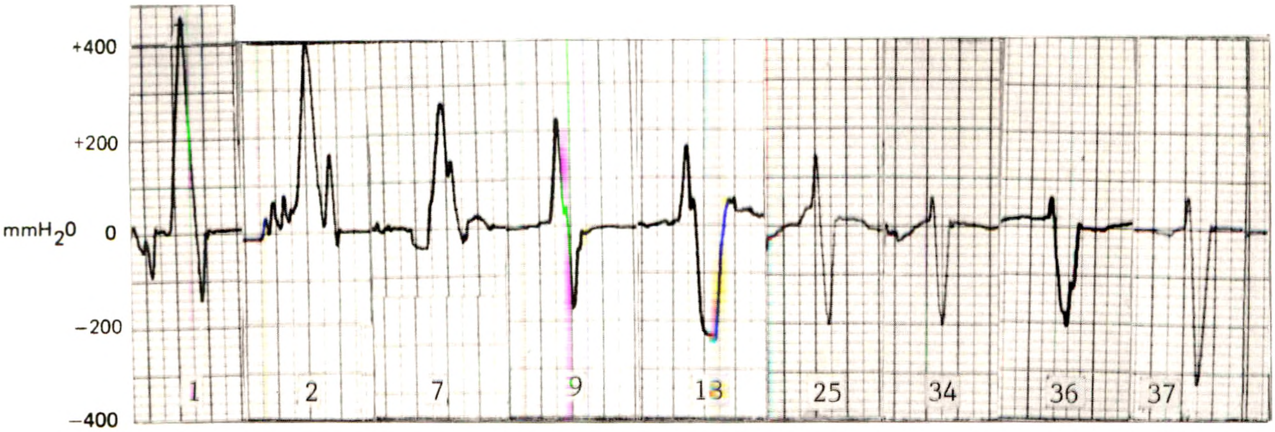

Fig 4. Various typical examples of nasopharyngeal pressure complexes. Patient numbers are indicated.

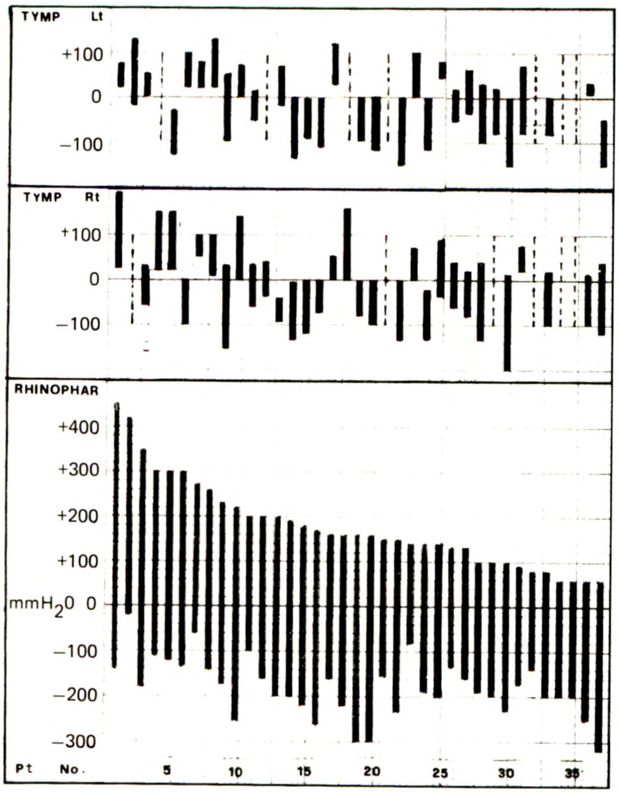

Fig 5. Summary of measurements of nasopharyngeal pressures obtained through catheters (bottom) and pressure variations in middle ear (top).

The mean negative pressure was −181 mm H_2O with an SD of 65. In certain subjects the total pressure gradients varied from 590 mm H_2O (patient 1) to 220 mm H_2O (Fig 5, patient 32).

The pressure waves obtained had a minimum of two phases. In patient 2 (Fig 4), a marked positive pressure was recorded together with a negative pressure component of −20 mm H_2O. In patient 37 (Fig 4) a negative pressure was recorded following a component positive pressure of + 60 mm H_2O. No statistically significant difference was found between men and women, and no age-dependent pattern emerged.

There is a noticeable uniformity of the appearance of the pressure curves in each patient tested (Fig 6A, patient 5). Variability is shown, however, when dry swallowing is compared to "wet," even in the same individual (Fig 6B). During a dry swallow a minute quantity of saliva is ingested inevitably. In most patients no difference was seen in the pressure curves between the dry swallow and deglutition using an amount of water. However, since differences may occur, for standardization of the measurements, all were performed wet. The quantity of water swallowed in a single bolus can, in some patients, affect the amplitude of the curves, as in patient 20 (Fig 6C). The ratio between the positive and the negative phases can also be affected by the quantity of water, as in patient 19 (Fig 6D).

A comparison was made between the shape of the curves obtained in the individual patients through nosepieces and through the catheters. Such a comparison is demonstrated in Fig 7 (patient 20). Curve A was obtained through the original ear tip (No. 20) of the middle ear analyzer applied to one nostril. Curve B was obtained after decongestion of nasal mucous membrane by spraying a 2% ephedrin solution. Curve C was obtained through a nosepiece that was developed for this purpose (Fig 3C,D). Curve D was obtained through the catheter placed into the nasopharynx. Curve E was obtained 1 month after successful nasal septal surgery. Measurement was obtained through the nosepiece after decongestion by 2% ephedrin.

The more precise methodology of pressure measurement often resulted in the demonstration of a greater absolute value of pressure difference and disappearance of the "rabbit ears" shape of the curve that was sometimes seen during measurement taken from the nostrils. A typical example is shown in Fig 7.

In Fig 8, pressure waves that developed in the nasopharynx during deglutition are shown on the left, and immediate tympanometric measurements are shown on the right. In patient 1 (Fig 8A), a nasopharyngeal pressure curve of + 450 to −140 mm H_2O was recorded. Following deglutitions with the catheters closed, two tympanometric measurements of + 25 mm H_2O (a,b) were obtained. These were followed by an increase of pressure in the right middle ear of up to + 190 mm H_2O (c). After further deglutitions with both catheters open, the fullness in the ear disappeared and tympanometric measurement again revealed a pressure of + 25 mm H_2O (d). The spectrum of pressure variations in the middle ear during the Toynbee maneuver in this patient was + 25 ⇌ + 190 mm H_2O. In patient 28 (Fig 8B), a nasopharyngeal pressure curve of + 100 to −190 mm H_2O was obtained. The initial right middle ear pressure (a) was + 30 mm H_2O. After deglutitions with the catheters closed, the patient had a sensation of fullness in both ears, and a pressure of −75 mm H_2O (b) was recorded. After further deglutitions with both catheters closed, values of −100 mm H_2O (c) and −130 mm H_2O (d) were recorded. On the next tympanometric measurement the middle ear pressure of −130 mm H_2O (e) dissipated and returned to a + 30 mm H_2O (f) when the patient swallowed with open catheters. Therefore, the spectrum of pressure variations in the middle ear was + 30 ⇌ −130 mm H_2O.

The summary of the measurements of nasopharyngeal pressures obtained through the catheters and pressure variations in the middle ear are illustrated in Fig 5. In patients 5 and 27, the spectrum of the pressure variations recorded in the middle ears was in the positive range in one ear, while in the opposite ear it was in the negative range. In 13

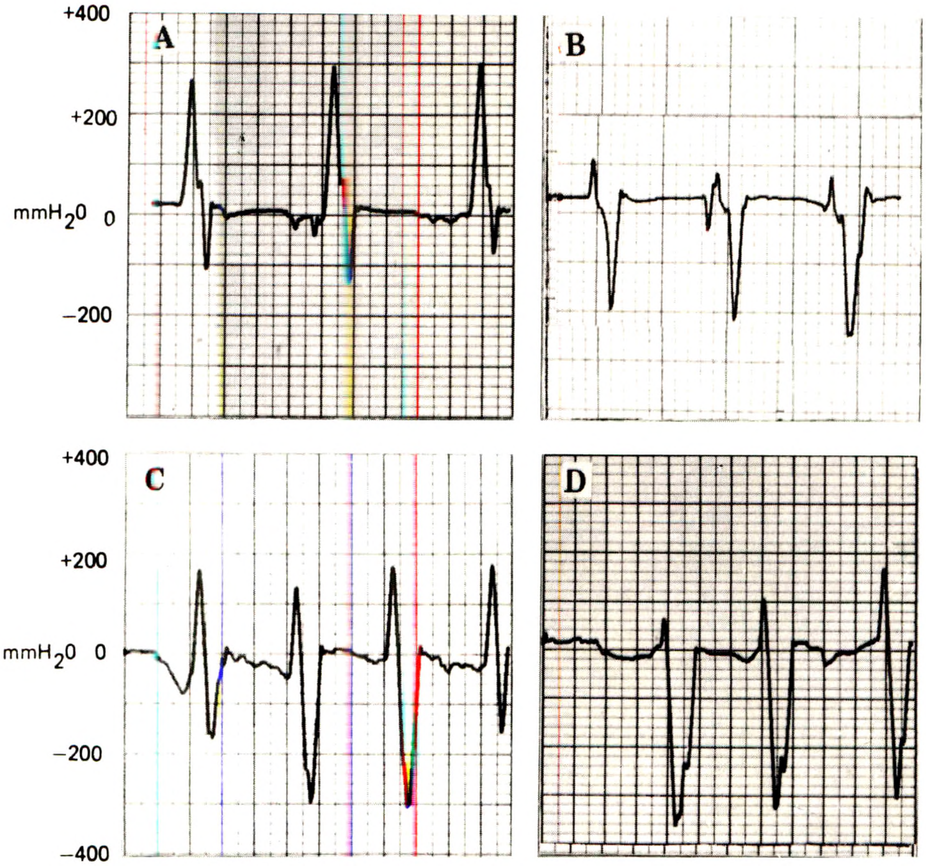

Fig 6. Noticeable uniformity of pressure curves in same individual. A) Patient 5 wet swallows, B) same patient on dry deglutition. Predominantly negative pressure wave is recorded. C) (Patient 20) Quantity of water swallowed in single bolus affected amplitude of curves. D) (Patient 19) Quantity of water swallowed in single bolus can affect ratio between positive and negative phases.

ears (approximately 17.5%) no pressure changes were obtained after repeated Toynbee maneuvers (Fig 5). Patient 4 presented sclerotic eardrums and two left retraction pockets. No variation of pressure in this middle ear was seen during the Toynbee maneuver (Fig 5).

DISCUSSION

In the present study surprisingly high pressure gradients were recorded in the nasopharynx during performance of the Toynbee maneuver. In previous studies published in the otolaryngologic literature, pressure variations in the nasopharynx ranged from + 140 to –280 mm H_2O.[6] Our measurements were obtained directly from the nasopharynx and not from the nostrils. No comments were made in previous studies concerning nasal airway resistance, which can alter the results of the measurements. Nasal airway resistance causes a pressure difference between the upstream (nasopharynx) and downstream (nostrils).[18-24] The nasal cavity distends during overpressure and retracts to its normal form when the pressure falls back to ambient level. Nasal airway resistance varies among individuals and in some can be seen to change from time to time.[16-18] The comparison between pressure curves obtained through nosepieces preoperatively and postoperatively and the curves obtained through the catheters proves that the pressure gradients that develop within the nasopharynx during the Toynbee maneuver are much higher than was previously known. Accu-

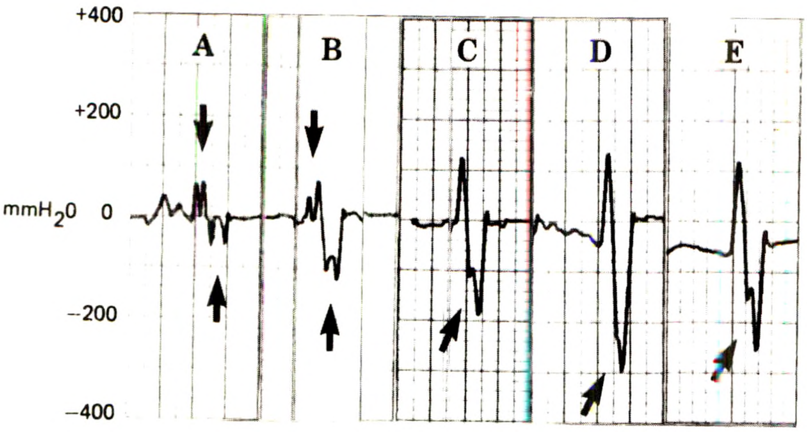

Fig 7. (Patient 20) Comparison of shape of curves. A) Curve obtained through No. 20 original ear tip of middle ear analyzer; B) after decongestion of nasal mucous membrane; C) through nosepiece shown in Fig 3C; D) through catheter; E) one month after successful nasal septal surgery through nosepiece after decongestion by 2% ephedrin.

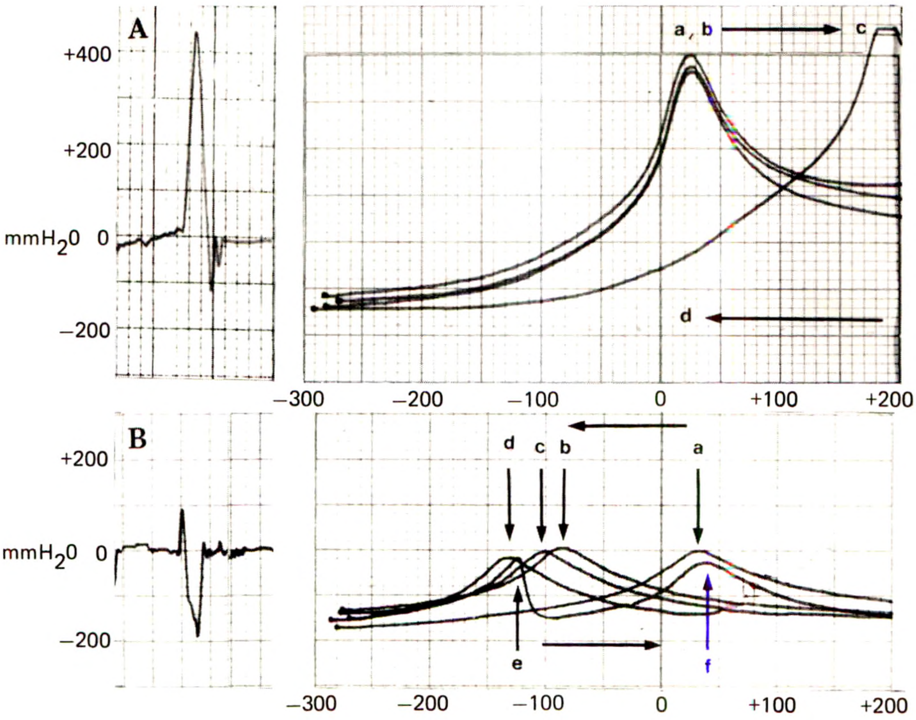

Fig 8. Pressure waves in nasopharynx during deglutition (left) and immediate tympanometric measurements (right). A) Patient 1, B) patient 28.

rate measurements can be made through catheters only. The causes of the previous imprecise measurements are probably due to the nasal airway resistance and perhaps the dead space between the nosepiece and the pressure transducer itself.

In the same individual there is usually a noticeable uniformity of the recorded curves that can be considered as the "fingerprints" of his/her first phase swallowing. Ingelstedt and Örtegren[10] have shown three types of pressure shape curves in the nasopharynx during the Toynbee maneuver: a purely negative type, a purely positive type, and a biphasic pressure complex. Our measurements show that the pressure wave complexes are always at least biphasic. In patient 2, for example, the negative phase is only −20 mm H_2O compared to the positive phase of +450 mm H_2O, producing a ratio of 1:22.5. In patient 37, the marked negative phase of pressure of −320 mm H_2O is preceded by a relatively small positive phase of +60 mm H_2O, producing a ratio of 1:5.3. Classification of the curves can be done as predominantly positive, predominantly negative, and biphasic, but with no clear-cut distinctions among these groups (Fig 5).

Our repeated tympanometric measurements demonstrate that during the Toynbee maneuver every subject has his/her own specific spectrum of middle ear pressure gradients (Fig 8). In some patients, however, the range of the pressure variations in one ear is parallel to the positive phase of the nasopharyngeal pressure curve, while in the second ear it is parallel to the negative phase (Fig 5; patients 5, 6, 36). Ingelstedt and Örtegren[10] have shown that during the Toynbee maneuver, if the eustachian tube opens, the middle ear pressure will change, depending upon the timing of the tubal opening and the pressure gradient in the nasopharynx. This opening may occur alternately in the positive and in the negative phases of the nasopharyngeal pressure curve.

Elner et al[11] report that the physiological range of the pressure difference between the middle ear and the nasopharynx needed for air passage through the normal eustachian tube during deglutition should be above +50 or below −50 mm H_2O. We used tympanometry for recording the middle ear pressure. Tympanometry is an indirect method that records only the final result of the complex movement of the eardrum during the same single maneuver and detects the final pressure before equalization. Ingelstedt and Örtegren,[10] using a direct method for recording tubal air passage, have shown that in several cases the middle ear cavity is insufflated and exsufflated with the same volume of air during one single Toynbee maneuver. Sometimes, also during our tests, patients complained about an annoying fullness in the ears that became milder or disappeared before tympanograms were made and negative results were obtained.

Perlman's[7] explanation for pressure fluctuations in the nasopharynx was that at the beginning of deglutition, the pressure rise is the result of the movement of soft palate and further contraction of pharyngeal muscles. The subsequent negative pressure was the result of dilatation of the oropharynx and hypopharynx followed by relaxation of the cricopharyngeal muscle. Since we did not measure volume and since all of our patients were adults, we cannot support or give evidence contrary to the theory of Bluestone et al[4] of nasopharyngeal size affecting its pressure gradients. Gramiak and Kelley[26] have shown that the pressure fluctuations are the result of the interplay among the soft palate, the pharyngeal constrictors, cricopharyngeus, and the tongue. Future research should be directed toward explanation of the variable pressure curves obtained during the Toynbee maneuver.

CONCLUSION

Since Toynbee's description of the maneuver named after him, the true sequence of events has been the object of constant research and dispute. Our study enlightens some aspects of this sequence. We show that pressure gradients in the nasopharynx are much higher than was previously thought. The biphasic nature of the development of the pressure curve is demonstrated. Every ear has its own spectrum of pressure variations during the maneuver. The pressure gradients in the nasopharynx due to chronic nasal occlusion in children with hypertrophied adenoids and rhinitis were implicated by some authors as being the direct etiopathogenic factor of middle ear disease.[3,13,14,27] Our findings can perhaps shed light on the prevailing and apparently opposed theories based on this assumption.

Children with a chronically obstructed nose can be classified into three groups. In the first, swallowing causes a reduction in middle ear pressure and repeated swallows further decrease the pressure. This results in atelectatic ears or secretory otitis media, as proposed by some authors.[3,13] In the second group, the Toynbee maneuver causes a rise in middle ear pressure. The insufflation of infected discharge from the nasopharynx to the middle ear could be the cause of recurrent otitis media as proposed by others.[14,27] The third group consists of patients in whom, during the Toynbee maneuver, the pressure gradients developed in the nasopharynx are of a low amplitude. These children can have marked nasal obstruction and may undergo surgery of the adenoids because of mouth breathing, but do not present middle ear disease. We have demonstrated the value of combined pressure equalization tubes with bilateral anterior nasal packing to eliminate high gradients of pressure in the nasopharynx and in consequence in the middle ear and to prevent the annoying Toynbee phenomenon.[28]

Two questions are raised: "What are the swallowing mechanisms that create different pressure waves in the nasopharynx among different subjects?" and "What are the factors that determine the specific spectrum of pressure variations in the middle ear during the pressure wave developed in the nasopharynx?" Further study of the physiology of the pharyngeal phase of deglutition and its relation to eustachian tube function is in progress.

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GERMAN SOCIETY OF OTO-RHINO-LARYNGOLOGY, HEAD AND NECK SURGERY

The 59th Annual Congress of the German Society of Oto-Rhino-Laryngology, Head and Neck Surgery will be held May 15-19, 1988, in Nuremberg, Federal Republic of Germany. For further information, contact Prof Dr K. Fleischer, Hittorfstr 17, D-5300 Bonn 1, Federal Republic of Germany.

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IMMUNOLOGIC RESPONSES AGAINST LIPOPOLYSACCHARIDE OF *HEMOPHILUS INFLUENZAE* IN PATIENTS WITH ACUTE SINUSITIS

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The serum antibodies against lipopolysaccharide of *Hemophilus influenzae* were measured in acute and convalescent phase sera from 30 patients with acute maxillary sinusitis using enzyme-linked immunosorbent assay. Levels of antibodies in the maxillary antral secretions were also measured. In convalescent phase sera from 15 patients with acute sinusitis due to *H influenzae*, there was a threefold, 1.5-fold, and threefold increase in the geometric mean titers of IgG, IgM, and IgA, respectively. In antral secretions, titers were significantly higher ($p<.01$) in culture-positive patients than in culture-negative patients for all antibodies. These data indicate that the immune system has the ability to respond systemically and locally with specific antibodies against lipopolysaccharide of *H influenzae*.

KEY WORDS — acute sinusitis, enzyme-linked immunosorbent assay, *Hemophilus influenzae*, lipopolysaccharide.

INTRODUCTION

The principal causative agents of acute maxillary sinusitis have been consistently reported to be *Hemophilus influenzae* and *Streptococcus pneumoniae*. *Hemophilus influenzae* has been isolated from approximately one third of all episodes of acute maxillary sinusitis, and a retrospective study showed an increasing occurrence of *H influenzae* in this disease.[1] For these reasons it seems to be important to investigate the host defense mechanisms against *H influenzae* in acute maxillary sinusitis. Although the capsular polysaccharide antigen of typeable *H influenzae* is accessible to host defense mechanisms, serologic typing of *H influenzae* isolated from maxillary sinus secretions has shown that less than 10% are type b and that the remainder are nontypeable.[2]

Two major classes of noncapsular surface antigens against which protective antibodies might be directed are outer membrane proteins and lipopolysaccharide (LPS). However, there are limited data on the immunogenicity of noncapsular antigens of *H influenzae*. Therefore, the present investigation was undertaken to present the results of serum and mucosal antibody responses of patients with acute sinusitis due to *H influenzae* against one of the noncapsular surface antigens, LPS.

MATERIALS AND METHODS

Bacteria. Strains of *H influenzae* serotypes a through f were supplied by the Institute of Medical Science, University of Tokyo. The strains were type a (ATCC 9327), type b (ATCC 9334), type c (ATCC 9007), type d (ATCC 9332), type e (ATCC 8142), and type f (ATCC 9833). Isolates of nontypeable *H influenzae* from the maxillary antral secretions of patients with acute sinusitis were also used.

Lipopolysaccharide. Lipopolysaccharide was extracted by the hot phenol-water procedure of Westphal et al[3] and isolated by repeated ultracentrifugation from water at 100,000 times gravity for 4 hours at 4°C. The final product was lyophilized, weighed, and suspended at a concentration of 1 mg/mL in distilled water containing 0.02% sodium azide. The preparations contained <0.05% capsule as determined by counterimmunoelectrophoresis[4] using each *H influenzae* type a through f polysaccharide antigen as a standard. The protein content of the preparations ranged from 1.0% to 5.2%. The limulus amebocyte lysate gelation produced by 6 to 14 ng of LPS from *H influenzae* types a through f was equivalent to that produced by 1 ng of reference LPS from *Escherichia coli* 0111:B4 (Difco), using the Pregel reagent kit (Seikagaku Kogyo Co, Ltd, Tokyo). Lipopolysaccharide preparations were analyzed in the discontinuous gel system described by Laemmli.[5] They migrated with low apparent molecular weights compared with reference LPS from *Salmonella typhimurium* (Sigma), a result indicating the absence of long O antigen chains (data not shown).

Subjects. Maxillary sinus secretions were obtained from 30 patients ranging in age from 7 to 40 years with acute maxillary sinusitis. None of them were taking antibiotics at the time the secretions were obtained for this study. Patients included in this study were observed to have no diseases other than sinusitis. Normal control sera were also obtained from 15 healthy subjects (six children and nine adults).

Collection and Storage of Specimens. A sample of sinus secretion (0.3 to 1.0 mL) was obtained by aspiration using a needle inserted into the maxillary antrum through the inferior nasal meatus. Fresh

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IgG, IgM, AND IgA ANTIBODY RESPONSE AGAINST LIPOPOLYSACCHARIDE (LPS) IN ACUTE AND CONVALESCENT PHASE SERA FROM PATIENTS WITH ACUTE SINUSITIS DUE TO NONTYPEABLE *H INFLUENZAE*

	IgG Antibody Titers		*IgM Antibody Titers*		*IgA Antibody Titers*	
Pt	*Homologous LPS*	*Polyvalent LPS*	*Homologous LPS*	*Polyvalent LPS*	*Homologous LPS*	*Polyvalent LPS*
1	< 100-500 (10.0)	< 100-300 (6.0)	< 100-310 (6.2)	< 100-300 (6.0)	200-1,200 (6.0)	300-1,700 (5.7)
2	500-3,300 (6.6)	400-3,500 (8.8)	780-620 (0.8)	800-700 (0.9)	150-280 (1.9)	170-300 (1.8)
3	690-1,000 (1.5)	550-900 (1.6)	220-320 (1.5)	350-400 (1.1)	460-760 (1.7)	400-600 (1.5)
4	< 100-500 (10.0)	100-650 (6.5)	600-690 (1.2)	600-1,300 (2.2)	< 100-960 (19.0)	< 100-900 (10.0)
5	200-550 (2.8)	150-350 (2.3)	650-1,000 (1.5)	500-900 (1.8)	< 100-400 (8.0)	< 100-300 (6.5)
6	< 100-850 (17.0)	< 100-550 (11.0)	< 100-300 (6.0)	< 100-260 (5.2)	< 100-580 (12.0)	100-800 (8.0)

Data are reciprocal antibody titer in acute phase serum/reciprocal antibody titer in convalescent phase serum. Numbers in parentheses show fold increase. Reciprocal titers of < 1:100 were defined as 50 for calculation of fold increases.

samples of maxillary sinus secretions without blood contamination were centrifuged at 986 times gravity for 15 minutes after dilution (1:2) in phosphate-buffered saline (PBS) after aerobic and anaerobic culturing. Paired sera were obtained. "Acute phase sera" and maxillary secretions were obtained within 7 days after onset of the symptoms, and "convalescent phase sera" were taken about 3 weeks later. All samples were kept at -70°C until assayed.

Serologic Methods. To measure antibody responses against LPS, the microimmunoassay was performed essentially as previously described.[6] In brief, polystyrene microtiter plates (Nunc No. 439454, Roskilde) were coated with LPS. A 0.3-mL aliquot of test sample diluted with PBS–1% bovine serum albumin (BSA) was transferred to each well of the antigen-coated plate. Horseradish peroxidase (HRP)-conjugated heavy chain-specific goat anti-human IgG (γ), IgM (μ), and IgA (α) (Cappel Laboratories, Cochranville, Pa) were diluted 1:1,000, 1:250, or 1:500 in PBS–1% BSA, respectively. A 0.3-mL volume of this solution was added to each, and the plates were incubated at 37°C for 1 hour. A 0.3-mL aliquot of a solution of enzyme substrate (2 g of 5-amino-2-hydroxybenzoic acid, 0.03 g of 4-amino-antipyrine, 1.7 g of KH_2PO_4, 3.5 g of K_2HPO_4, 10 μL of H_2O_2) was added. The reaction was stopped after incubation for 1 hour at 37°C by adding 25 μL of N NaOH to each well. The absorbance was measured with a Corona microplate two-wave length photometer ($\mu_1 = 450$ nm, $\mu_2 = 660$ nm). The adult serum pool was used as a reference to standardize. Dilutions of 1:1,000, 1:250, and 1:500 of this serum pool produced an absorbance value of 0.25 after incubation for more than 45 minutes with a substrate for IgG, IgM, and IgA assays, respectively. When the mean absorbance of the reference wells reached more than 0.25, the absorbance values of test sample dilutions were measured. For each test sample, a titration curve was obtained by plotting absorbance as a function of the reciprocal dilution using a semi-logarithmic scale. The assay was essentially linear for dilutions producing an absorbance value of 0.17 to 0.90. Titers were determined graphically as the intercept of the 0.25 absorbance end point. Each assay included appropriate antigen-negative and sample-negative wells as controls.

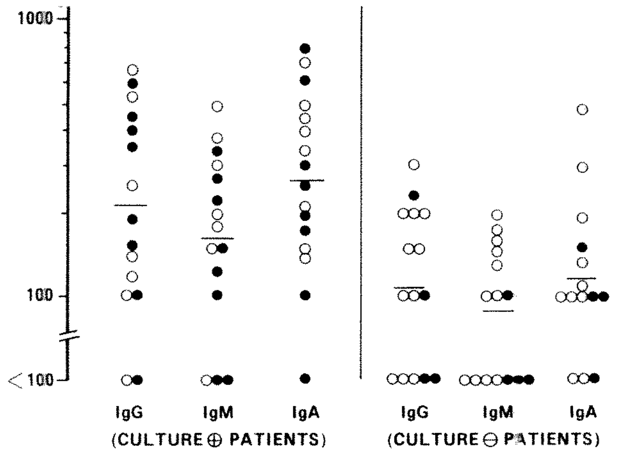
RESULTS

Antibody Responses Against Homologous and Heterologous Lipopolyaccharide Preparations. Acute and convalescent phase sera were available from six patients whose isolates of nontypeable *H influenzae* were used for preparation of LPS. Titers of IgG antibodies against LPS in acute phase sera ranged from < 1:100 to 1:690, titers of IgM antibodies against LPS ranged from < 1:100 to 1:780, and titers of IgA antibodies against LPS ranged from < 1:100 to 1:1,200 when assayed with homologous LPS (see Table).

Five of the six patients showed a sixfold or greater increase in titers of IgG, IgM, or IgA antibodies in convalescent phase sera. Four of these five patients showed increases in titers of all antibody classes against LPS.

For these six patients, serum antibody titers were also determined with preparations of LPS extracted from typeable *H influenzae* (serotypes a through f). The LPS pool was used to titrate the above sera. All five patients who showed fivefold or greater increases in serum titers of IgG, IgM, or IgA antibodies against LPS from their own isolates also responded with a fivefold or greater increase in titers against polyvalent (LPS pool) LPS (see Table). Similarly, none of the paired sera showing less than a fivefold increase in titers of IgG, IgM, or IgA antibodies against homologous LPS showed significant increases in titers of antibodies against the polyvalent LPS.

Antibody Titers Against Polyvalent Lipopolysaccharide. The polyvalent LPS was used to measure the antibody titers of the nine remaining patients



Titers of IgG, IgM, and IgA antibodies against lipopolysaccharide in antral secretions of culture-positive and culture-negative patients. For all antibodies, titers were significantly (p<.01) higher in secretions of culture-positive patients than in those of culture-negative patients. Closed circles — children, open circles — adults.

with acute sinusitis due to *H influenzae* whose isolates were not available, the titers of the 15 patients with acute sinusitis whose isolates were not *H influenzae*, and the titers of control children and adults. There were no significant differences between the geometric mean titers of antibodies against LPS in sera from the healthy children and adults and the titers in sera from culture-negative patients with acute sinusitis. A significant antibody response against LPS was seen when the convalescent phase sera from culture-positive patients was compared with the corresponding acute phase sera. In convalescent phase sera from 15 patients with acute sinusitis due to *H influenzae*, there was a threefold, 1.5-fold, and threefold increase in the geometric mean titers of IgG, IgM, and IgA, respectively.

Specific antibodies against LPS were also found in the maxillary antral secretions (see Figure). For all type-specific antibodies, titers were significantly higher (p<.01) in the antral secretions of culture-positive patients than in those of culture-negative patients. IgA was the predominant immunoglobulin class of anti-LPS antibodies in the antral secretions, because the ratios of serum versus antral IgA were significantly higher than those of serum versus antral IgG.

DISCUSSION

Denny[7] showed that the human or animal tracheal epithelium disintegrated after incubation with *H influenzae* because of its endotoxic activity. The LPS of *H influenzae* is presumed to have a toxic effect on the tracheal epithelium and then induces a bronchial obstruction.[8] Therefore, it is important to study the antibody responses against LPS of *H influenzae*. However, there are limited data on the immunogenicity of LPS in humans.[9] The results of the present investigation demonstrate that enzyme-linked immunosorbent assay is a useful addition to the wide range of currently available methods for detection of antibodies against LPS of *H influenzae*. To date, most serologic tests have been done with antigens extracted from a single strain of *H influenzae*. However, the use of antigens from a single strain of *H influenzae* would presumably limit the sensitivity of an assay because recent findings have demonstrated microheterogeneity among strains of *H influenzae*.[10,11] Therefore, a polyvalent coating antigen was fabricated with equivalent amounts of LPS from six different serotypes. When the polyvalent antigen was tested with sera from *H influenzae* culture-positive patients, the antigen-antibody reactions or extinction values observed with the polyvalent antigens were equivalent to the values obtained with the corresponding monovalent antigen.

The predominant immunoglobulin classes of anti-LPS antibody in serum were IgG and IgM. In contrast, the predominant immunoglobulin class of anti-LPS antibody in the antral secretions was IgA. The relative proportion of class-specific antibodies in the antral secretions as compared with those in the serum supports our contention that anti-LPS mucosal antibodies result mainly from secretion rather than from transudation. These results are similar to those found in an earlier study of antibodies against outer membrane vesicles of *H influenzae* in patients with acute sinusitis.[6] The antibody titers in saliva and nasal secretions were not examined in the present study.

We also found the presence of relatively high levels of naturally acquired antibodies against LPS in control children and adults. The source of these naturally acquired antibodies is unknown, but they may be the result of exposure to cross-reacting antigens in the normal flora of the respiratory tract or intestine. Titers were significantly higher in the antral secretions of culture-positive patients than in those of culture-negative ones. This response may be due to a booster effect. The antibody responses against LPS both in the convalescent sera and in the antral secretions suggest that the immune system has the ability to respond systemically and locally with the specific antibodies against LPS of *H influenzae*. Current research to quantify local antral antibodies should add to our understanding of the protective role of mucosal antibodies.

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XIV WORLD CONGRESS OF OTORHINOLARYNGOLOGY

The XIV World Congress of Otorhinolaryngology will be held June 11-16, 1989, in Madrid. For further information, contact J. J. Alvarez-Vicent, MD, Secretary General, Villanueva 11, 28001 Madrid, Spain; phone (34) 1 431 26 92.

Ann Otol Rhinol Laryngol 97:1988

X-RAY STUDY OF THE MONTH

ORBITAL CELLULITIS WITH ABSCESS FORMATION CAUSED BY SINUSITIS

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A 12-year-old boy presented with a 1-day history of swelling of the right periorbital area and a 1-week history of rhinorrhea and sneezing. Physical examination revealed him to be febrile to 39°C, and swelling of the right superior and inferior eyelids was detected. There was no evidence of proptosis, and there was full range of motion of the extraocular muscles. He was admitted and immediately given intravenous oxacillin, 200 mg/kg/day. Over the next 18 hours, the patient developed proptosis, and for assessment of the orbital inflammatory process, a computed tomograph was obtained. On the basis of the CT examination and the clinical findings, the patient was taken to the operating room, where he underwent a right external ethmoidectomy, sphenoidotomy, and drainage of a medial orbital subperiosteal abscess. Cultures obtained from the abscess and right ethmoid sinus revealed α-hemolytic streptococci, staphylococci, and group B streptococci.

RADIOGRAPHIC FINDINGS

The sinus films obtained on admission demonstrated bilateral opacification of the ethmoid and maxillary sinuses. A CT scan was performed in the axial and coronal projections after the infusion of an intravenous contrast medium. This examination demonstrated an inflammatory mass located within the medial aspect of the right orbit along the lamina papyracea (see Figure, A). The mass revealed a low density area consistent with an abscess and a lateral enhancing rim secondary to a thickened, inflamed, and displaced periosteum. The medial rectus muscle on the right was displaced laterally and was obliterated by the inflammatory mass. The globe was displaced forward and laterally as evidenced on the axial and coronal CT scans. The intraconal fat, including the optic nerve and the remaining extraocular muscles, was preserved. There was a diffuse increase in density in both ethmoid sinuses and both maxillary antra, along with swelling in the nasal cavities (see Figure). There was no evidence of bone destruction, and no intracranial abnormality was detected.

DISCUSSION

In 60% of patients with acute orbital inflammation, sinusitis has been found to be the cause.[1] The ethmoid sinus is the predominant source of the infection, followed by the maxillary antrum, frontal sinus, and sphenoid sinus, or there may be involvement of several sinuses. An understanding of the regional anatomy explains the association of sinus disease with orbital infection. Over half the circumference of the orbit consists of a thin plate of bone separating the orbital cavity from the adjacent sinuses (orbital floor, lamina papyracea, and floor of the frontal sinus). The orbital periosteum (periorbita) is the only soft tissue barrier between the orbital cavity and the ethmoid sinus. This fibrous membrane is adherent to the lamina papyracea at the suture lines and is elevated relatively easily from the bone. Infection from the ethmoid sinus may spread into the subperiosteal space through the lamina papyracea via dehiscences or a localized osteomyelitis in the bony wall. Spread of infection also may occur from the sinuses into the orbits via valveless anastomosing veins or through the perivascular spaces. Orbital cellulitis can be subdivided into 1) preseptal inflammation, 2) preseptal inflammation with a subperiosteal infiltrate or abscess, 3) orbital cellulitis involving the extraconal and intraconal spaces, and 4) an orbital abscess in the intraconal and extraconal compartments.[2] In the presence of acute orbital infection, an adequate ophthalmologic examination of the eye may be difficult or impossible.

Computed tomography contributes significantly to the diagnosis and management of these patients by demonstrating the precise location and extent of the inflammatory process within the orbit, associated sinus disease, and intracranial complications such as orbital apex syndrome,[3] cavernous sinus thrombosis, cerebritis, extradural empyema, subdural empyema, and brain abscess.[4,5] Axial and coronal contrast CT sections with infusion of a contrast medium are the preferred radiographic techniques for the assessment of an orbital inflammatory pro-

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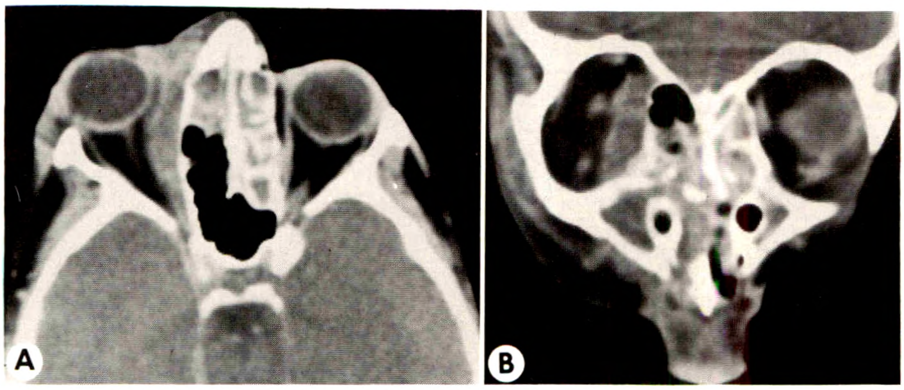

Computed tomographs. A) Axial section reveals mass along medial wall of right orbit with low density center and enhancing displaced periosteal lining. Note swelling in anterior lid and canthal area. Medial rectus muscle is obliterated. B) Coronal section demonstrates swelling in both nasal cavities and increased swelling in both ethmoid sinuses and maxillary antra. Medial orbital inflammatory mass is seen in coronal plane. Note low density center and enhanced displaced periorbita.

cess.[6] Swelling of the preseptal orbital soft tissues, caused by lid and conjunctival edema, is indicated on CT by a diffuse increase in density and thickening of these structures on the axial planes. Extension of the infectious process into the postseptal region is reflected by increased density in the extraconal space along the medial orbital wall. The medial rectus muscle is displaced laterally, often enhances slightly, and may be thickened from the inflammatory edema. There is displacement of the periosteum adjacent to the lamina papyracea laterally into the orbital cavity. Enhancement of the periorbita occasionally occurs, indicated by an enhancing rim along the medial border of the subperiosteal infiltrate (see Figure). Pus accumulation in the subperiosteal space is reflected by a longitudinal-shaped low density area, as demonstrated in our case. Loss of the lamina papyracea, secondary to localized osteomyelitis, is manifested by demineralization of the bony wall or partial bony loss.

A medial subperiosteal inflammatory mass or abscess produces anterior and lateral displacement of the globe, while an infiltrate superiorly from frontal sinusitis displaces the globe forward and inferiorly. In most instances, the inflammatory process is limited to the subperiosteal space; it rarely extends into the intraconal space of the orbital cavity. An abscess also may develop in the upper lid and medial canthal area as an extension of the subperiosteal abscess. Extension of the inflammatory process into the intraconal space is manifested on the CT by an ill-defined infiltrate with obliteration of the extraocular muscle and optic nerve. An abscess, reflected by a low density area with rim enhancement, may develop on rare occasions in the intraconal space. This is indicated clinically by marked proptosis and a decrease in visual acuity from either compression on the optic nerve or compromise of the blood supply to the optic nerve. Osteomyelitis of the bony structures of the orbit is a rare finding in orbital cellulitis secondary to sinusitis. In our experience, chronic osteomyelitis is caused by foreign bodies, especially wood, that are lodged in the orbit. The presence of air that may be visible within the inflammatory infiltrate is caused by anaerobic bacteria or leakage of air from the sinuses into the orbit. If the inflammatory infiltrate is adjacent to the globe, thickening of the scleral-uveal coat occurs. This widening is caused by a collection of inflammatory cells in Tenon's space.

Prior to the antibiotic era, orbital infection was associated with a high mortality and morbidity. Appropriate management and close observation, as exemplified in this case, can result in a successful outcome. Clinical management of orbital infection generally includes intravenous antibiotic therapy. If there is a progressive decrease in vision along with proptosis (usually indicative of spread or expansion of a subperiosteal abscess), surgical intervention is indicated.[7] Computed tomography has been helpful in guiding the surgeon in the operative approach and also in providing supportive evidence for surgical intervention.

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Ann Otol Rhinol Laryngol 97:1988

PATHOLOGY CONSULTATION

SURGICAL MARGINS IN SQUAMOUS CELL CARCINOMAS

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Positive or negative surgical margins of excision cannot predict the clinical course of patients with squamous cell carcinomas of the head and neck. Local recurrences are increased in frequency and number when invasive or in situ carcinoma or severe dysplasia is present at the margins. Histologic grade of the carcinoma has no influence. In patients with negative margins, 2- and 5-year survivals are dependent on the clinical stage and size of the primary tumor.

An axiom of "curative" surgery for localized cancer in the head and neck is that complete excision of the neoplasm be performed. One of the putative indicators of completeness of the surgical removal is the margin of uninvolved tissue around the excised neoplasm. How generous the margin should be has not, and likely cannot, be defined for all forms of cancer — or for that matter, selected classes of malignancy. Tumor sites, anatomic restrictions, presumed biologic characteristics of the cancer, and the respective advantages of conservation and extended surgery are just some of the factors in the predetermination of adequate margins of resection.

There is little doubt that gross residual cancer will yield local persistence and nearly always an increased mortality. The clinical significance of retained microscopic cancer, on the other hand, has not been defined, and there are few pertinent retrospective studies of the problem.[1-5]

For squamous cell carcinomas of the upper aerodigestive tract, there is a site dependency not only in the ability of the surgeon to obtain tumor-free margins, but also in the biologic significance of involved or uninvolved limits of excision. This variation relates more to the biologic and epidemiologic environment, microanatomic and macroanatomic, of the sites than to any intrinsic histologic differences in the squamous cell carcinomas themselves. These factors also strongly imply that one cannot extrapolate margin significances from carcinomas of the glottis to carcinomas of the oral cavity and pharynx.

It has been claimed that microscopic accuracy of an adequate surgical margin is at least 50%,[1] at least as judged by local recurrences. In part, this rather low assessment is due to pathologic and clinical (surgical) difficulties coincident with the evaluation of preoperatively irradiated tissues and submucosal extension or skip areas. In part, also, must be the contributing factor of lack of close cooperation between surgeon and pathologist.

What constitutes positive or negative surgical margins lacks standardization and certainly precision. Irrefutable microscopic evidence is the presence or absence of invasive carcinomas at the line of resection. Intraepithelial carcinoma at the margins has also been considered as positive. The effects of closeness to a margin and of severe dysplasia at the margin on recurrences and prognosis have not been systematically evaluated. Indeed, neither of these factors is easy to assess. Severe dysplasia remains a highly subjective pathologic impression and as such is capable of being overdiagnosed or underdiagnosed. Measurement is more objective, but its reliability varies with the conditions of measurement. Postremoval and postfixation shrinkage renders these measurements inferior to an in situ, frozen section–monitored estimation of distance from the carcinoma. Using excised uterine cervical tissue, Boonstra et al[6] have indicated that a formalin-fixed, embedded, and sectioned specimen has a total shrinkage of about 15% of the fresh tissue. Formalin fixation produces an overall mean shrinkage of 2.7%, and the dehydration, clearing, and paraffin embedding account for about 12.5%. The actual sectioning of the tissue block and mounting do not increase shrinkage.

Given optimum conditions (surgical and pathologic), what are the prognostic implications of the microscopic determination of the adequacy of local removal of squamous cell carcinomas of the oral cavity and pharynx? It has long been the author's opinion that histologic grade is subservient to size or T stage of a squamous cell carcinoma as a prognostic indicator. Depending on the skill of the surgeon and the anatomic location of the carcinoma, T stage may not seriously impair the possibility of securing microscopically free surgical margins.[2,3,5] The significance of size, however, bears heavily on local recurrences, and more so on 2- and 5-year survivals, even when there are surgically free margins. Furthermore, it is to be accepted that a rather constant number of carcinomas (5% to 10%) will resist the

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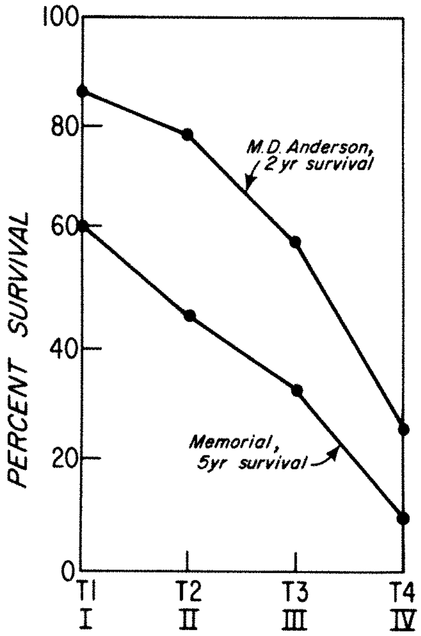

Survival of patients with negative surgical margins for mucosal squamous cell carcinomas of head and neck treated surgically at M. D. Anderson Hospital, Houston (grades T1 through T4), and Memorial Sloan Kettering Cancer Center, New York (stages I through IV). (Survival curves plotted from data presented by Byers et al[3] and Looser et al,[2] respectively.)

surgical goal of clear margins, regardless of their apparent T stage.[1-3]

Based on available information, it appears that lesional tissue within 0.5 cm of a surgical margin, be it severe dysplasia or in situ or invasive carcinoma, places a patient at nearly an equal risk for local recurrence.[2] Failure of local control is not inevitable with such positive margins, but is associated with a nearly 80% incidence of recurrent disease. In the study by Looser et al,[2] 71% of patients with positive margins manifested recurrence at the primary site, compared with only 32% of patients with negative margins. Byers et al[3] report similar findings. Extralaryngeal sites with significant recurrence rates after negative margin surgical excision are those in the oral cavity and pharynx. Looser et al[2] rank the palate, tonsil, and pharynx including the pyriform sinuses the highest, with primary site recurrences of 41.6%, 41.5%, and 37.2%, respectively.

If the surgical margins are negative, there is certainly no assurance of successful local control. In fact, clinical T stage appears to be a more predictable determinant: the smaller the carcinoma with free surgical margins, the higher the local control rate. In like manner, survival of patients with free margins is related almost linearly to the T stage of their carcinomas (see Figure).

The prognostic implications of a positive microscopic margin also relate to stage of the disease. Stage for stage, there is an increased incidence of recurrences at the primary site — certainly a not unexpected correlation. Survival of 2 and 5 years and longer, however, is more dependent on stage, especially for patients with stage III and IV malignancies.[2,3]

A significantly lower incidence of local recurrences is reported in patients with primary squamous cell carcinomas of the larynx who have positive surgical margins following conservation laryngeal surgery. Thirty-nine of 111 patients undergoing hemilaryngectomy, studied by Bauer et al,[4] had positive surgical margins (close, gross, and microscopic involvement). Only seven of the 39 developed a local recurrence. Four of the remaining 72 (5.6%) with uninvolved margins developed local recurrence. Inexplicable as these data may seem, they cannot be ignored, and they give support to the notion that there is considerable site dependency to results. Patients who are candidates for conservative laryngeal surgery have early-stage carcinomas and hence more favorable prognoses. The disposition of submucosal lymphatic drainage, or lack thereof, in the laryngeal glottis very likely also plays a role in the lower incidence of locoregional recurrences, irrespective of the status of the margins.

Vikram et al[7] have indicated a decrease in the failure rate at the primary site with postoperative irradiation and found more recurrence in patients whose margins were microscopically involved. Despite the seemingly random quality of the status of surgical margins, they still provide therapeutic and prognostic guidelines.

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LETTERS TO THE EDITOR

To the Editor:

In their retrospective analysis of postlaryngoscopy airway complications (Airway Complications from Laryngoscopy and Panendoscopy. *Ann Otol Rhinol Laryngol* 1987;96:691-4), Dr Richard Hill et al tried to "derive some insights" but offered conclusions that only can lead to more complications and fatalities. In their series, more than 90% of the patients who required reintubation had T3 or T4 lesions in the laryngopharynx. Every experienced head and neck surgeon knows that when tumors in this region are bulky and friable, accurate assessment of their extent is often difficult. Many such patients have no preoperative signs of upper airway obstruction, a fact that may lull the otolaryngologist and the anesthesiologist. Repeat "passes" by the anesthesiologist followed by those of the endoscopist create a bloody, edematous airway. Occasionally, the airway is totally lost in the process of attempted intubation, and a crash tracheotomy is necessary.

If the following principles are adhered to, a relatively safe, uncomplicated endoscopy can be accomplished:

1. Communicate with the anesthesiologist about the location and size of tumor, to minimize intubation trauma. When intubation or endoscopy are traumatic, then a prophylactic tracheotomy is done at the end of the procedure.

2. If clinical evaluation reveals that one side of the glottis is obscured by a bulky friable tumor, then a tracheotomy is performed under local anesthesia prior to endoscopy.

Any risks associated with a tracheotomy, such as stomal recurrence, are far outweighed by the possibility of losing one life from a preventable upper airway obstruction. Besides, T3 and T4 lesions of the laryngopharynx should be treated with radiation as well as surgery. Resorting to such measures as laser and keeping a resident in the recovery room just to avoid an orderly tracheotomy does not make medical sense at all.

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To the Editor:

We appreciate the comments of Dr Deeb, who states that the conclusions of our paper will lead to increased complications and fatalities. The conclusions of our paper documented the airway risk factors associated with panendoscopy and laryngoscopy in order to decrease morbidity and mortality associated with these procedures. We feel that if the otolaryngologist is cognizant of these airway risk factors, he or she will be better prepared to deal with an airway complication arising from endoscopy. Dr Deeb stated that more than 90% of patients who required reintubation had a T3 or T4 lesion. This statement is incorrect. Only four of the 13 endoscopy patients who needed recovery room reintubation (31%) had a T3 or T4 laryngopharyngeal tumor. As noted in our paper, even patients with T1 or T2 laryngeal tumors who undergo endoscopy with biopsies can develop airway compromise (69% of the recovery room reintubation group).

Although Dr Deeb makes a good point in that the otolaryngologist should communicate with the anesthesiologist prior to the intubation of patients with laryngopharyngeal tumors, we take issue with his aggressive airway management of patients with T3 and T4 tumors. In the Discussion section of our paper, we describe how the airway is managed in patients undergoing panendoscopy and laryngoscopy at the Albany Veterans Administration Medical Center. We do not feel that all patients with T3 or T4 tumors should have a tracheotomy as part of their endoscopy. The airway management of patients with T3 and T4 laryngeal tumors should be individualized according to the patient's airway risk factors, the skills of the surgeon and anesthesiologist, and the facilities of the recovery room and the intensive care unit of the hospital.

Richard S. Hill, MD
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BOOK REVIEWS

Atlas of Ear Surgery

Andrew W. Miglets, Michael M. Paparella, and William H. Saunders. 4th ed. Hard cover, illustrated, indexed, 471 pages 1986. CV Mosby, St Louis, $86.

This atlas is a beautifully illustrated, easy to follow guide to techniques of otologic surgery. The illustrations are anatomically accurate and sequentially constructed in accordance with the steps in the procedure. The drawings are neither oversimplified nor unnecessarily detailed, and the legends are helpful to the reader.

The volume begins with a chronologic outline of the development of otology and is rich with historical information (This is the only chapter with a bibliography, and the latest entry was published in 1961; the authors feel that more recent developments have not withstood the test of time.)

Subsequent chapters cover temporal bone anatomy and dissection, giving pointers on instrumentation and step-by-step illustration of major procedures that can be performed in a temporal bone laboratory. Surgical procedures begin with operations of the external ear, including otoplasty and reconstruction of the auricle, followed by surgical management of neoplasms and cysts and of infections of the ear. This section includes helpful tips on controlling bleeding and special precautions important in mastoid surgery. Complications of mastoiditis, including intracranial disease, are also described. The section on surgery for Meniere's disease may be somewhat misleading, since procedures that are much less commonly used are given equal coverage with frequently used procedures such as the endolymphatic shunt. Facial nerve surgery is generally well covered with good diagrams, although detail is lacking on isolating the greater auricular nerve.

Almost one third of the book is devoted to an excellent chapter on surgery for conductive deafness. Congenital malformations of the ear canal and middle ear are described, middle ear exploration is outlined, and a number of methods for ossicular chain reconstruction are presented, including various prostheses. Management of perilymphatic fistulas and ossicular fixation, fenestration, myringoplasty and tympanoplasty, and tympanoplasty with mastoidectomy are discussed, and a sizeable portion of the chapter describes stapedectomy, special cases, and complications.

Neurotology is the subject of the final chapter, which illustrates approaches to the internal auditory canal for reduction of temporal bone fractures with facial nerve injury, vestibular nerve section, and acoustic neuroma excision. Singular nerve section and cochlear implant procedures are the concluding topics.

Familiarity with this book will contribute to the learning experience of otolaryngologists in training and in general practice. Neurotologists may find it helpful in teaching procedural techniques and, quite possibly, in apprising patients of the approach to their operations.

L. Clark Simpson, MD
Dennis G. Pappas, MD
Birmingham, Alabama

The Ear: Diagnostic Imaging. CT Scanner, Tomography and Magnetic Resonance

Jacqueline Vignaud, Caroline Jardin, and Lawrence Rosen. Hard cover, illustrated, indexed, 365 pages, 1986. Masson, New York, $95.

This volume is an independent printing of a portion of the large

Traité de Radiodiagnostique, a French radiologic encyclopedia. The text is a compendium of otologic radiology produced by a group of 27 European and nine American radiologists under the direction of Jacqueline Vignaud and one of her associates at Fondation Ophthalmologique Rothschild in Paris, as well as Lawrence Rosen, a California radiologist. Many of the authors took part in the Eleventh International Congress of Radiology in ORL, which was chaired by Dr Vignaud.

The book reminds me of the years during which otolaryngologists had only a wide variety of plain film projections and polytomographic images available to study the temporal bone. There is transition to modern techniques of high resolution computed tomography, but many pathologic entities are illustrated only by the older tomographic techniques. Magnetic resonance imaging is described in an appendix-like final chapter and is not integrated into the body of the text. The reader also must be careful of the MRI technique descriptions, because they are the reverse of American designation in which we list repeat time (TR) first, then time of echo (TE). In this text TE is first and TR second.

The text is very uneven because of the variety of writing styles of each group of authors. English with "French" spelling is also evident, as in "mixt tumors." Spelling errors are prevalent. In spite of these editorial oversights, there are some gems. Chapters on temporal bone embryology and anatomy are particularly well done, as are descriptions of sectional anatomy and high resolution CT, both of which are accompanied by sparkling photographic illustrations. The section on the facial nerve canal is also well done, but accompanied by many polytome illustrations.

The book probably is of most use to the new otoradiologist or otologist who has not lived and worked through the years of plain films and tomography, but who wishes to follow the historical development of radiologic examinations of the temporal bone. The book is probably of less value to the experienced otologist or otoradiologist unless he or she wishes to review CT and be introduced to the scope of MRI. A useful high point of the text is the comprehensive bibliography.

KENNETH D. DOLAN, MD
Iowa City, Iowa

Voice Problems in Children

D. Kenneth Wilson. 3rd ed. Hard cover, illustrated, indexed, 400 pages, 1987. Williams & Wilkins, Baltimore, $28.50.

This third edition is organized much like the second, although the text has been increased from 238 pages to over 400. The examination section has been enlarged from two chapters to three, and an additional chapter has been included on the treatment of voice disorders. A new chapter, "The Professional Voice User," has been added. This is a good reference book for the student of voice disorders and the practicing speech pathologist. The book is particularly well referenced, and a helpful glossary has been included.

The first four chapters deal with the definitions, incidence, and causes of voice problems. Chapter Two defines organic causes of voice problems and is enhanced with drawings by Frank Netter. Organic changes that occur when the voice is abused are described, and in the final chapter in this section, functional causes for voice problems and contributing factors are discussed. Research data are integrated and some clinical cases presented to demonstrate various conditions. In the next section, the author discusses evaluation procedures, emphasizing the need for a team approach and the reason for various examinations. He provides a good outline for obtaining pertinent information from the case history. Ten examination forms to profile the voice in all its parameters are included, and the need for audio and video recordings of the voice is emphasized as a means of developing baseline data of the voice and associated behaviors. From these data an appropriate diagnosis can be made and therapeutic goals formulated. Research and methodology to evaluate pitch, loudness, quality, resonance, and voice abuse are reported. Pitch charts and maximal phonation times for ages 1 through 18 years and both sexes are included. The final section of the book consists of therapeutic procedures for the various voice problems identified in children and adults. A new chapter for the professional voice user emphasizes good vocal hygiene. In the final chapter, voice habituation and family involvement are discussed in relationship to the treatment of voice disorders.

This text appears to be most appropriate for the student of speech pathology. It is a good reference text for the speech pathologist who does not consistently work with voice disorders. Although emphasis is placed on voice problems in children, certainly much is also appropriate for adults who have vocal dysfunction.

DUANE VAN DEMARK, PHD
Iowa City, Iowa

Clinical Otology and Audiology

G. G. Browning. Soft cover, illustrated, indexed, 272 pages, 1986. Butterworth, Stoneham, Mass, $45.

The author, a senior lecturer in otolaryngology at the University of Glasgow, states that his purpose in writing yet another textbook on otology and audiology is to present "a practical guide to help otolaryngologists diagnose, investigate and thereafter manage patients with otological conditions." He is often absorbing in reporting observations from his personal otologic practice, and he makes a worthwhile contribution in bringing attention to the significant percentage of false-positive responses to some currently used diagnostic/evaluative procedures. Overall, however, the text lacks unity and will be frustrating to the experienced otologist and confusing to the beginning physician. Hearing aid evaluations, for example, are not quantified audiometrically; the idea that surgical management of serous otitis media is indicated only if the thresholds are poorer than 25 dB (bilaterally) for longer than 6 months is controversial; and the author's suggestion that patients with vestibular neuritis may proceed to develop vertebrobasilar ischemia, chronic labyrinthitis, or multiple sclerosis is puzzling. The author vividly but haphazardly documents his points of conflict with currently accepted standard practice protocols.

DENNIS G. PAPPAS, MD
LYNN CARMICHAEL, MSC
Birmingham, Alabama

Trauma of the Middle Ear: Clinical Findings, Postmortem Observations and Results of Experimental Studies

M. Strohm (translated by Jürgen Tonndorf). Volume 35 in *Advances in Oto-Rhino-Laryngology*. C. R. Pfaltz, editor-in-chief. Hard cover, illustrated, indexed, 254 pages, 1986. Karger, Basel, Switzerland, $74.25.

Reports of clinical and basic studies evaluating trauma of the middle ear continue to increase in importance today, as head and neck trauma becomes more commonplace. This book provides insight into various aspects of middle ear trauma using clinical evaluations, postmortem findings, and x-ray findings.

The book is divided into five parts: 1) injury of the tympanic membrane, 2) lesions of the ossicular chain, 3) endocranial complications of lesions of the middle ear and injuries of the facial nerve, 4) cholesteatoma of traumatic origin, and 5) posttraumatic perilymphatic fistula.

As Dr Strohm reports on the cases he studied, the prevailing site of rupture of the tympanic membrane, regardless of the cause of injury, was the anterior inferior quadrant; the most frequent ossicular chain lesion was subluxation of the incus; facial nerve injury occurred in 88% of transverse and 55% of longitudinal fractures; a small number of posttraumatic cholesteatomas resulted from various types of injuries; and rarely recognized ruptures of the round window membrane appeared to occur in conjunction with blunt skull trauma. The reader must keep in mind, however, that variations are inherent in lesions resulting from injuries, and each patient presents unique manifestations.

Although essentially no new information is presented by the author, he has succeeded in presenting known facts through practical and new observations. Topics relating to the five parts of this book include etiology, signs and symptoms, and therapy. The transition is orderly and precise, with meticulous attention to detail. The reference section provides the reader with an exceptionally complete overview of the work that has been done in the area of middle ear trauma.

Jürgen Tonndorf has accomplished a monumental task in translating this text from the original German. In so doing, he has made available a wealth of knowledge about ear trauma. Anyone desiring to learn all that is currently known about ear trauma could do no better than to consult this comprehensive work.

Dennis G. Pappas, MD
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Neurobiology of Hearing: The Cochlea

R. A. Altschuler, R. P. Bobbin, and D. W. Hoffman, eds. Hard cover, illustrated, indexed, 490 pages, 1986. Raven Press, New York, $98.50.

Bekesy was the first to report on the specificity of the traveling wave as it approaches the auditory nerve. This book focuses on the physical and chemical aspects of that process, which are fundamental to understanding the hearing mechanism.

A distinctive feature of this book is its precise orientation, which should stimulate discussions and new deductions concerning the physiopathology of the ear. Current assessments of the neurobiology of the cochlea are followed by a description of the afferent and efferent neuronal connections between the cochlea and the brain. Concluding sections describe the clinical application of this information. The work is thorough and the information is clearly presented in terminology that is readily comprehensible. These results may constitute a turning point in the conceptualization of the hearing mechanism. The subject is intriguing and warrants the serious attention of otologists.

Dennis G. Pappas, MD
Birmingham, Alabama

Complications in Otolaryngology–Head and Neck Surgery

Richard J. Wiet and Jean-Bernard Causse, eds. Vol 1. *Ear and Skull Base.* Hard cover, illustrated, indexed, 207 pages, 1986. BC Decker, Philadelphia.

The editors have compiled a list of the difficulties that may be encountered in temporal bone surgery from the experiences of a number of esteemed otologic surgeons. This publication was not intended to be a complete text, presenting all data and details relevant to particular conditions. Rather, the reader is led directly to the appropriate application of a specific procedure and treatment of possible preoperative and postoperative complications of ear surgery.

The format used in this publication is an excellent vehicle to achieve the editors' purpose. Each chapter is devoted to the surgical treatment of a specific ear condition. This allows the contributors an ample opportunity to develop the variations in criteria for the procedure, the technique itself, and the possible consequences involved. For instance, in the chapter on surgery for control of vertigo, the author thoroughly pursues the options in surgical procedures for vertigo patients, pointing out the significance that the cause, the status of the hearing, and the patient's age and general health have in selecting the procedure to be used.

The format may well be the most outstanding feature of the book, as it allows sought-after solutions to be located easily. Those authors who deviated from the format tended to include ambivalent, textbook-type information that diluted the cohesiveness of the work. Fortunately, most of the contributors used the format well. Those who elaborated on surgical techniques chosen to minimize complications gave relevant additional information.

The concluding chapter of this volume is on legal defense in malpractice suits. The inclusion of such information in a text on complications encountered in surgical procedures is quite reasonable; however, this topic cannot be covered adequately in a few brief paragraphs.

The editors have assembled a wide range of current knowledge and present it in a compact, well-written volume that will be an invaluable teaching or review source for clinicians.

Dennis G. Pappas, MD
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Birmingham, Alabama

The Practicing Physician's Approach to Headache

Seymour Diamond and Donald J. Dalession, eds. Hard cover, illustrated, indexed, 24 pages, 1986. Williams & Wilkins, Baltimore, $38.50.

Drs Diamond and Dalession have performed a valuable service in presenting this work on headaches, especially to those who suffer from this malady. Unfortunately, there always will be medical practitioners who lack empathy, are overextended by their practice, or for some other reason will not pursue the cause of such a "mundane" complaint as a headache and will be satisfied to treat it symptomatically. Although many patients may respond favorably to such a therapeutic regimen, for others it is to be hoped that they will find the services of a physician who is familiar with this text.

Drs Diamond and Dalession present a text that is to be applied, rather than just read or used as a reference book. They facilitate this experience by beginning with a classification of headaches into three simple categories: vascular headaches, muscle contraction headaches, and traction and inflammatory headaches. They have prevailed upon their ten contributors, each with expertise in cephalalgia, to use these same classifications in their chapters.

It is commendable that all of the authors stick to proven medical facts and do not contrive causes and effects. Migraine headaches, which are too often made the scapegoat by physicians who are not inclined to investigate, are adequately covered without being overexposed. Headaches caused by muscle contraction, such as eye strain, are sufficiently covered without being encumbered by details. It is disappointing, however, that the otolaryngologists who contributed to the text chose to address headache resulting from acoustic neuroma, which is rare, rather than the frequently seen headache secondary to Meniere's disease.

This is an instructive and informative manuscript that will intrigue the physician who wishes to expose and treat the underlying cause of headache.

Dennis G. Pappas, MD
Birmingham, Alabama

Occupational Hearing Conservation

Maurice H. Miller. *The PRO-ED Studies in Communicative Disorders*, Harvery Helpern, series ed. Soft cover, illustrated, 87 pages, 1986. Pro-Ed, Austin, Tex, $7.

This book is one in a series of monographs in which the most recent developments in occupational hearing conservation (OHC) are discussed. The author makes no attempt to present the pathophysiology of hearing loss or acoustic trauma. Rather, the text covers the legislative background of OHC programs, the major aspects of these programs, certification programs for those implementing or directing OHC programs, available hearing protectors, and educational programs for employees.

The author has presented a well-written, concise text that primarily should be of interest to students and practitioners in speech and hearing sciences who are interested in the current status of OHC programs as well as their mandates, recommendations, and their implementation.

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INSTRUCTIONS TO AUTHORS

Send manuscripts to Editor Brian F. McCabe, MD, Department of Otolaryngology-Head and Neck Surgery, University of Iowa Hospitals, Iowa City, IA 52242. Original manuscripts dealing with clinical and scientific aspects of otolaryngology, bronchoesophagology, head and neck, maxillofacial and plastic surgery, audiology, speech pathology, and related specialties will be considered for publication.

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INDEX TO ADVERTISERS

Albany Medical College	21a
American Society of Pediatric Otolaryngology	10a
Boston Medical Products, Inc	4a
Burns Clinic Medical Center, PC	third cover
Children's Hospital of Boston	10a
Clinica Popular	third cover
C. V. Mosby Company, Ltd	17a
Grason-Stadler	7a
Hall Surgical	8a-9a, 18a-19a
Hood Laboratories	12a
House Ear Institute	20a
Iowa, University of	11a, 15a
Johns Hopkins Health System	14a
Karl Storz Endoscopy-America, Inc	second cover, 1a
Long Island Jewish Medical Center	21a
Massachusetts, University of	22a
Medical Associates Health Center	21a
Michigan, University of	12a
Montgomery, William W.	14a
Mount Sinai School of Medicine (CUNY)	15a
NeuroCom International, Inc	2a
Norwich Eaton Pharmaceuticals, Inc	third cover, fourth cover
Palm Beach Medical Group, Inc	21a
Santa Barbara Medco, Inc	13a
SUNY Health Science Center	14a
University Hospital of Jacksonville	14a
Voice Foundation	12a
Washington University	15a
Willmar Medical Center	22a
XOMED Inc	16a
Zimmer	8a-9a, 18a-19a
Zurich, University of	10a

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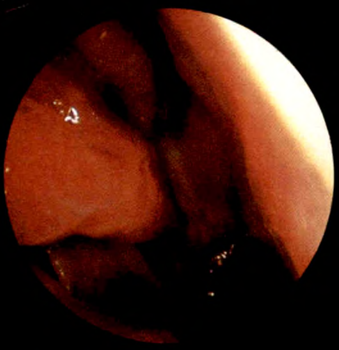
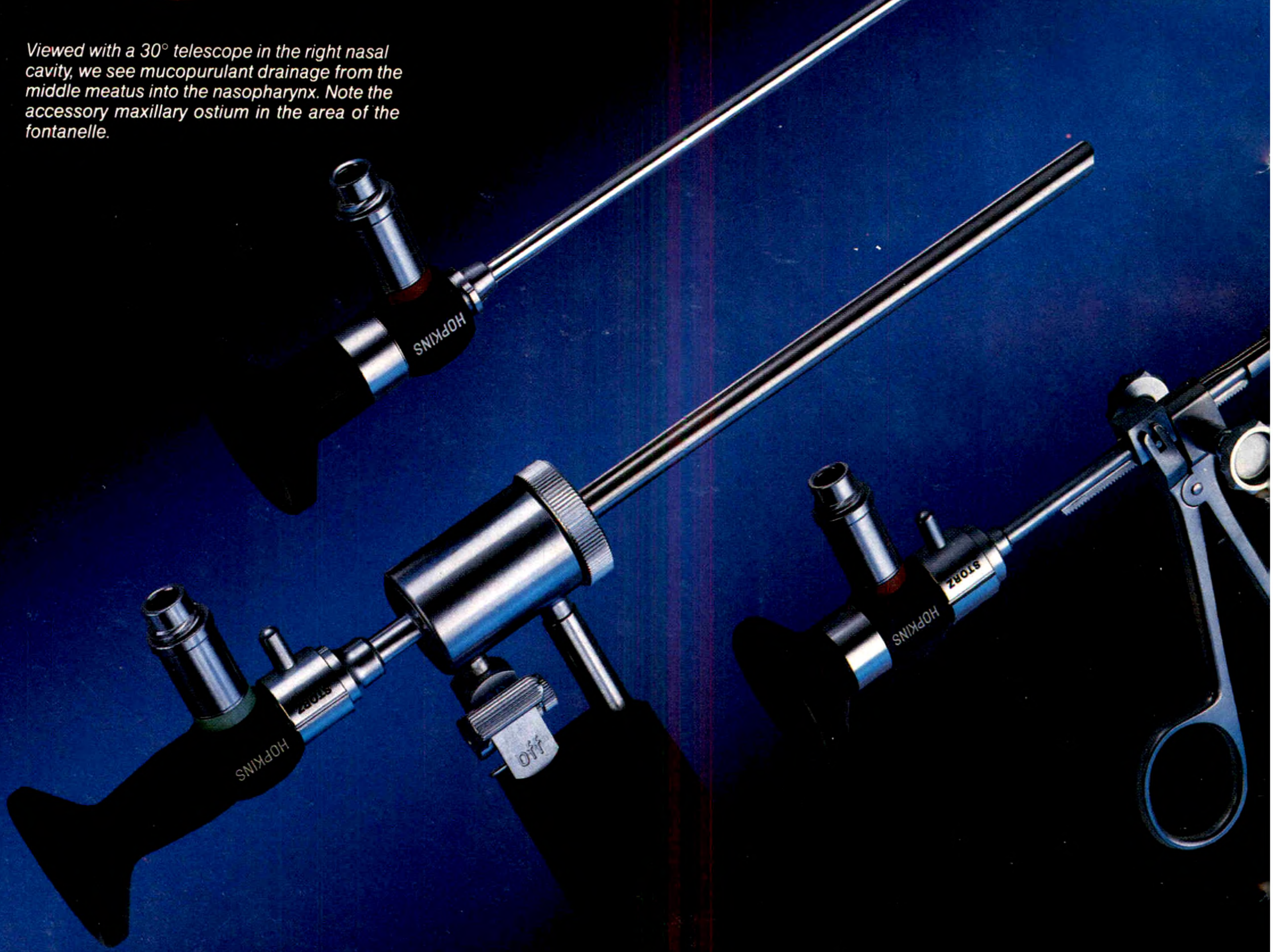


Viewed with a 30° telescope in the right nasal cavity, we see mucopurulant drainage from the middle meatus into the nasopharynx. Note the accessory maxillary ostium in the area of the fontanelle.



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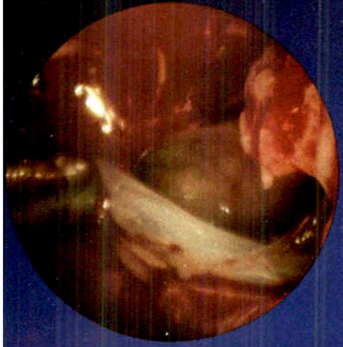

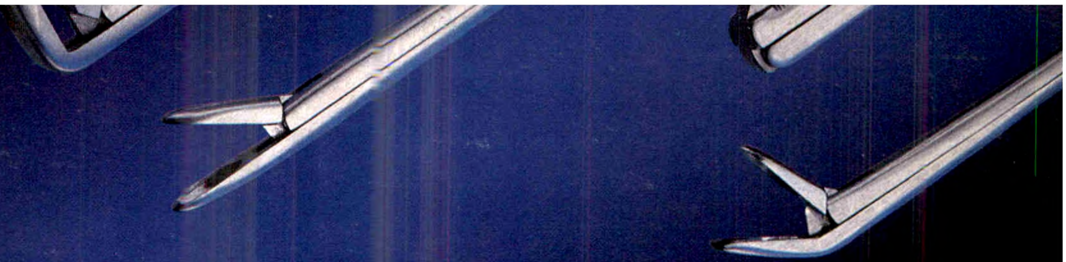

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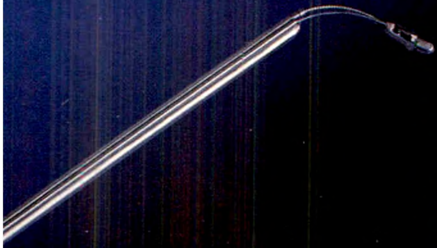

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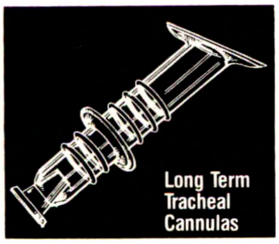
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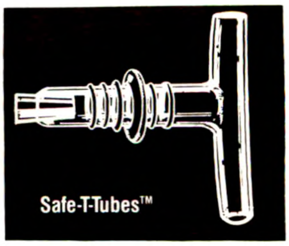
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VOLUME 97 MAY-JUNE 1988 NUMBER 3

CONTENTS

PART 1

Patent Eustachian Tube in the Underaerated Middle Ear: A Paradox
Richard A. Buckingham, MD ... 219

Carbon Dioxide Laser Surgery in Otorhinolaryngology: Pulsed Beam Versus Continuous Wave Beam
Rudolf Grossenbacher, MD; Rudolf Sutter, MD ... 222

Facial Muscle Reinnervation: A Comparison of Neuromuscular Pedicle With Direct Nerve Implant
Samuel J. Hall, FRCS; Ronald E. Trachy; Charles W. Cummings, MD ... 229

Technique for External Repositioning of the Paralyzed Vocal Cord With Silastic Implant
J. Ramón Escajadillo, MD ... 234

Protocol for Management of the Interposition Cartilage Graft Laryngotracheoplasty
C. A. J. Prescott, FRCS(Eng) ... 239

Comparison of the Microbiology of Group A and Non-Group A Streptococcal Tonsillitis
Itzhak Brook, MD, MSc; Paula Yocum ... 243

Clinical Investigations of Adductor Spastic Dysphonia
David E. Hartman, PhD; James H. Abbs, PhD; Balaji Vishwanat, MD ... 247

Acquired Ultrastructural Alterations of Respiratory Cilia and Clinical Disease. A Review
John J. Ballenger, MD ... 253

Effects of Elevated Intranasal Temperature on Subjective and Objective Findings in Perennial Rhinitis
Dov Ophir, MD; Yigal Elad, PhD; Aaron Fink, MD, PhD; Elza Fishler, MD; Gabriel Marshak, MD ... 259

Comparison of the Intrasubject Repeatability of Auditory Brain Stem and Middle Latency Responses Elicited in Young Children
Kevin T. Kavanagh, MD; William D. Domico, PhD; Patricia L. Crews, MS; Virginia A. McCormick, MS ... 264

Hearing Impairment in Relation to Viscoelasticity of Middle Ear Effusions in Children
Yuichi Majima, MD; Yukiyoshi Hamaguchi, MD; Keisuke Hirata, MD; Kazuhiko Takeuchi, MD; Atsuhito Morishita, MD; Yasuo Sakakura, MD ... 272

Dysphonia Caused by Forestier's Disease
Isaac Gay, MD; Joseph Elidan, MD ... 275

Relationship of Eustachian Tube Bony Landmarks and Temporal Bone Pneumatization
N. Wendell Todd, MD; W. Stephen Martin, MD ... 277

Reversible Conductive Hearing Loss in Mice
Linda J. Hood, PhD; Douglas B. Webster, PhD ... 281

Chronic Herpetic Laryngitis With Oropharyngitis
Paul N. Karnauchow, MD, FRCP(C); William H. Kaul, MB, FRCS(C) ... 286

Vascular Effects of Neuropeptides on Nasal Mucosa
Keiichi Ichimura, MD; Hiroyuki Mineda, MD; Atsuro Seki, MD ... 289

In Vitro Electrophysiologic Studies on Nasal Airway Receptors of the Rabbit
Tadahiko Hoshino, MD ... 294

Effects of Bacterial Endotoxin on Ciliary Activity in the Tubotympanum
Yoshihiro Ohashi, MD; Yoshiaki Nakai, MD; Yusuke Esaki, MD; Hiroshi Ikeoka, MD; Hiroyuki Koshimo, MD ... 298

Epithelial Distribution in the Human Fetal Larynx
Nicholas D. Stafford, MB, FRCS; Stephen J. Davies . . . 302

Synaptic Bodies in the Different Rows of Outer Hair Cells in the Guinea Pig Cochlea
R. Swetlitschkin, MD; L. Vollrath, MD . . . 308

Ultrastructure of Mucous Blanket in Otitis Media With Effusion
Masashi Inagaki, MD; Yasuo Sakakura, MD; Takeshi Shimizu, MD; Yuichi Majima, MD; Kotaro Ukai, MD . . . 313

Collagen Components of Bovine Fetal and Guinea Pig Cochlear Bone and Human Stapes
T. J. Yoo, MD, PhD; Thomas M. Chiang, PhD; Saryu Dixit, PhD; Naohiro Sudo, MD; Taizo Takeda, MD; Tsukasa Ishibe, MD; Jerome Seyer, PhD . . . 318

Study of Humidification Potential of a Heat and Moisture Exchanger in Tracheotomized Dogs
Charles M. Myer III, MD; John S. McDonald, DDS; Richard N. Hubbell, MD; John Stith, MD . . . 322

Imaging Case Study of the Month. Enlarged Jugular Foramen
Donald P. Mueller, MD; Kenneth D. Dolan, MD . . . 326

Pathology Consultation. Alveolar Soft-Part Sarcoma
John G. Batsakis, MD . . . 328

Letters to the Editor . . . 330

Book Reviews . . . 330

Instructions to Authors . . . 13a

Index to Advertisers . . . 14a

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Symposium on Biochemical and Immunochemical Aspects of Otitis Media
Steven K. Juhn, MD; G. Scott Giebink, MD; Editors . . . Supplement 132

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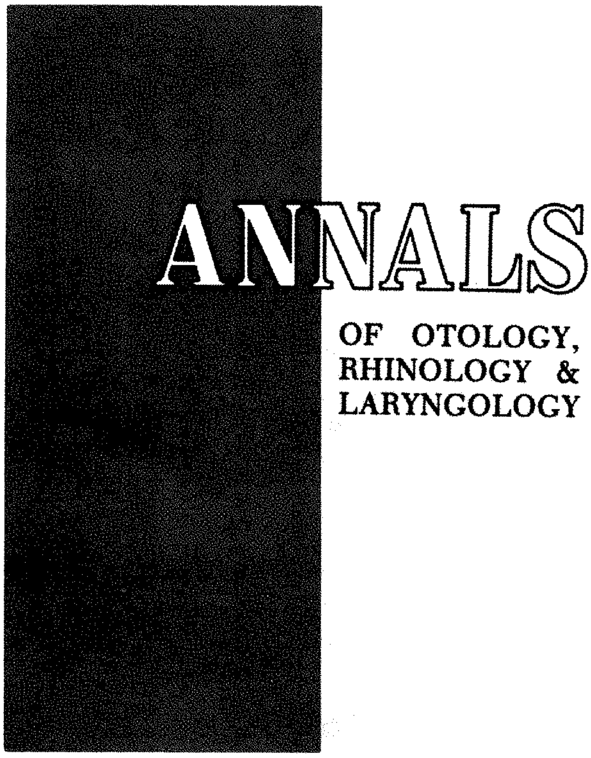

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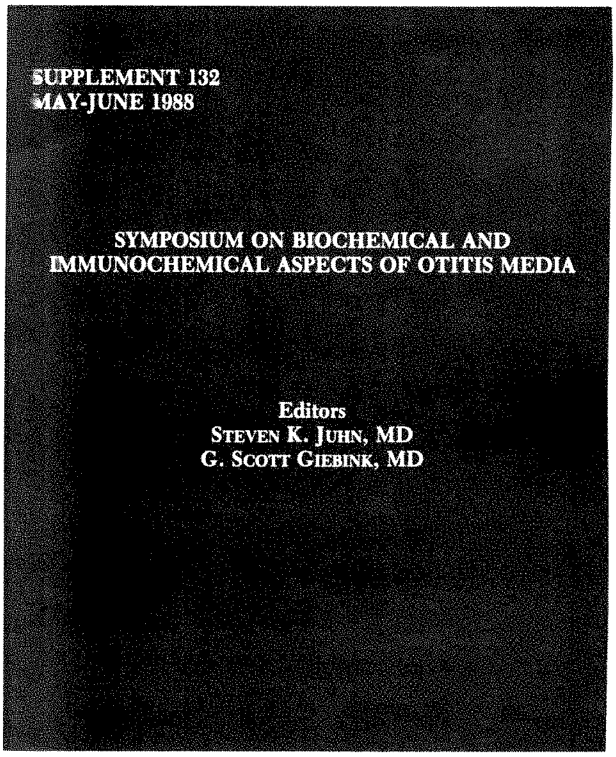

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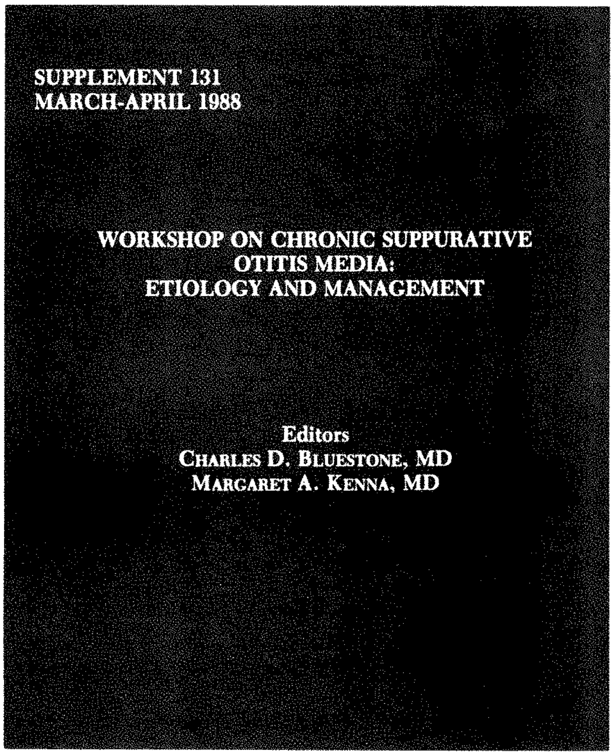

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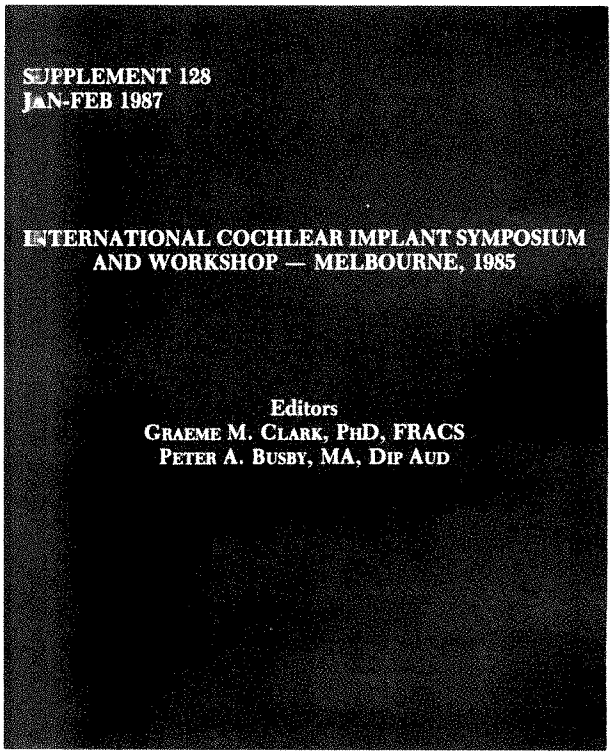

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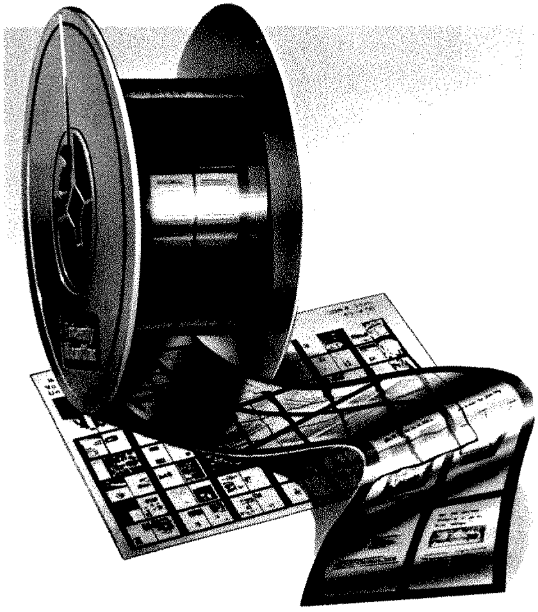

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PATENT EUSTACHIAN TUBE IN THE UNDERAERATED MIDDLE EAR: A PARADOX

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Secretory otitis media, middle ear atelectasis, and retraction type cholesteatomas are the most frequently occurring chronic middle ear diseases; and eustachian tube obstruction and the generation of negative or less than atmospheric middle ear pressure is said to be an essential factor in the pathogenesis of these diseases. It has been found that habitual sniffing causes high degrees of negative middle ear pressure in diseased ears; this finding demonstrates eustachian tube patency rather than obstruction. Ears intubated for chronic secretory otitis media, middle ear atelectasis, and cholesteatoma were examined to identify patent eustachian tubes. More than one third of the patients aspirated a solution into the middle ear with one or more sniffs by aspirating air from their middle ears, demonstrating eustachian tube patency rather than obstruction.

KEY WORDS — eustachian tube, middle ear, otitis media, sniffing.

Underaeration of the middle ear (ME) is important in the pathogenesis of chronic ear diseases such as secretory otitis media (SOM), atelectasis of the ME, and retraction type cholesteatoma. In the first two of these diseases, decreased ME pressure is demonstrated consistently by tympanometry and is corrected by intubation. Buckingham and Ferrer[1] have reported on prevention and correction of early atelectatic cholesteatomas with intubation.

Most authorities[2-4] cite eustachian tube (ET) obstruction and attendant absorption of oxygen in the ME and mastoid as the cause of ME underaeration and negative or less than atmospheric ME pressure. Magnuson[5] recently observed that many patients with ear disease associated with ME underpressure generate high degrees of stable negative ME pressure by sniffing, and actually aspirate air from their MEs through the ET. Magnuson[6] stated that patients able to suck air from their MEs had abnormally patent ETs, since the ET is said to be closed except during swallowing and purposeful opening. He recorded negative ME pressures as great as −1,000 mm H_2O using an elaborate laboratory technique.

To confirm Magnuson's observations of ET patency in ear disease in an everyday clinical setting, the author devised a simple method of testing the effects of sniffing on ME pressures. A minute amount of an oil-based ear medication was instilled into ME ventilation tubes in ears previously intubated to determine how many patients aspirated the medication into the ME and demonstrated ET patency by drawing air from the ME into the nasopharynx. To avoid patient selection bias, patients with intubated MEs affected by diseases caused by underaeration of the ME were examined consecutively as they came to the clinic for routine follow-up examinations.

PROCEDURE

From Jan 3, 1985, to June 30, 1986, 673 intubated ears were studied with the patients in the supine and erect positions. Some ears were tested more than once. The flanged ME ventilating tubes were approximately 1 cm long, with an inside diameter of 0.86 mm and an outside diameter of 1.27 mm. The tubes had been in place for at least 1 week to insure an airtight seal at the tympanic membrane (TM). A drop of Terra-Cortril (Pfizer, New York), a sterile, oil-based medication, was placed within the lumen of the ear speculum. Using a 2-mm Billeau ear loop, a film of the oily solution was transferred to the distal end of the polyethylene tube. This formed a column of solution 1.5 to 2.0 mm, approximately 1.6 μL. No aspiration of the external canal was done, to avoid developing a negative ME pressure or altering external canal temperature before sealing the tube with oil.

While supine, the patients were instructed to sniff alternately through one nostril and then the other while occluding the opposite nostril.

When oil was aspirated into the ME, indicating decreased ME pressure and ET patency, the test was considered completed. If the oil column did not move, the patient was elevated to a sitting position and the sniffs were repeated.

When no movement of the oil column occurred with the patients either supine or erect, the tube was aspirated gently with a suction tube to determine the patency of the ventilation tube. Failure of the TM to move inward when negative pressure was

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RESULTS OF SNIFFING OF TERRA-CORTRIL

	Secretory Otitis Media *N (%)*	*After Modified Mastoidectomy and Atticotomy* *N (%)*	*Middle Ear Atelectasis* *N (%)*	*Children < 16 Yrs** *N (%)*
Decreased middle ear pressure	176 (43)	51 (33)	40 (35)	57 (52)
No change in middle ear pressure	229 (56)	103 (67)	74 (65)	53 (48)
Total ears tested	405	154	114	110
Decreased middle ear pressure in erect position only	49 (28)	10 (20)	5 (13)	

*Includes children with secretory otitis media, modified mastoidectomy and atticotomy, or middle ear atelectasis.

applied to the tube identified obstructed and nonfunctioning tubes.

RESULTS

The results are reported as causing a decreased ME pressure or no change in ME pressure, since a decrease in ME pressure aspirated the solution into the ventilating tube and ME (see Table).

Patients who sniffed and decreased ME pressure had patent ETs in the test ear at the time of the test procedure. Between 33% and 43% of patients of all ages tested aspirated fluid into the ME of the ear examined.

The average age of the patients was 43 years. One hundred ten of the 673 ears tested were in children less than 16 years old. In 57 or 52% of these 110 ears, air was aspirated from the ME. The ME tubes were in place in these 57 ears an average time of 12 months. Three ears were tested 1 week after intubation, and 16 ears were tested 1 month after intubation.

The position of the patient appeared to have some effect on ET patency to sniffing. Of 176 ears with SOM tested, air was aspirated in 49 or 28% only after the patient assumed the erect position, the ET being closed when the patient was tested in the supine position. According to Rundcrantz,[7] Perlman[8] in 1939 noted the tendency of patent ETs to close when patients assumed a recumbent position.

DISCUSSION

The three ear disorders that form the basis of this study all are associated with chronic negative or less than atmospheric ME pressures. The ears with SOM all had fluid (thick, thin, or gluey) for at least 3 months before intubation. Likewise, the atelectasis of the ears with deeply retracted, and at times inpocketed, atrophic TMs was a chronic disorder of months' or years' duration.

The cholesteatomas had been treated with modified radical mastoidectomies and atticotomies. In both procedures, the ME segments were intubated routinely at the time of surgery. Cholesteatomas are examples of the most chronic ME underaeration.

As mentioned, many cholesteatomas develop from atelectatic pockets in the pars flaccida or pars tensa, and since such atelectatic pockets are often corrected by early intubation, underaeration of the ME is perhaps the most important factor in the cause of the disorder. The ME segment of a modified radical mastoidectomy is excluded from the mastoidectomy cavity, but at the same time the ME segment remains in continuity with the ET and is open to atmospheric pressure via the polyethylene tube. In the atticotomy patients, the lateral attic wall was removed and the cholesteatoma matrix retained over the usually intact ossicular chain. In these cases, the bony canal wall is intact and the matrix covering the ossicles lies in contact with the skin of the superior wall of the external canal. Thus the ME, epitympanum, antrum, and mastoid cavity are closed to the external ear and atmosphere, except through the polyethylene tube through the TM.

The present theory of the ET's function in normal ME ventilation is based on the assumption that O_2 is absorbed at a constant and continuous rate, causing a decreased ME pressure that is equilibrated during swallowing when the ET opens and air is aspirated to ventilate the ME. Without O_2 absorption and the development of a negative ME pressure, there would be no differential pressure gradient between the nasopharynx and the ME, and no ME ventilation could occur. Eustachian tube obstruction — anatomic, functional, or inflammatory — is thought to prevent resupply of air to the ME and to result in underaeration and ME disease.

In this study, in 33% to 43% of the diseased ears of all patients and in 52% of the diseased ears of children under 16 years of age, negative ME pressure was generated by sniffing. This unexpected demonstration of ET patency is unaccounted for by the generally accepted theory that the ET is normally closed except during swallowing. This is evidence that the ETs in these ear were patent and that ET obstruction and O_2 absorption was a highly unlikely cause of the decreased ME pressure causing the ear disease, because the ET could not be patent and obstructed simultaneously.

These data support Magnuson's conclusion that sniffing can and does evacuate ME gases and decreases pressure in many diseased ears. The technique reported here is a simple clinical procedure that can be performed in any otologist's office.

The finding that many patients who have had mastoidectomies aspirate ME gases illustrates the necessity of postoperative ME ventilation to prevent recurrent ME atelectasis and cholesteatoma. This is especially important after atticotomy.

Using a refined laboratory technique, Falk and Magnuson[9] found in one series that 63% of ears with SOM generated negative ME pressure. With the tympanometer, Falk[10] tested 100 subjects with normal ears and found that only 14% could generate negative pressure by sniffing.

The intubated SOM cases in this study were all chronic, and if ET obstruction were the cause of the effusion we would have to assume that intubation somehow corrected the obstruction. Similarly, the atelectatic ears were chronically retracted, and the atelectasis was present for several months. It is unlikely that tubal function would improve by the mere act of ventilating the ME in 40 of the 114 ears that generated negative ME pressure by sniffing.

Demonstrating that it is possible to aspirate air from the ME by sniffing does not in itself disprove that O_2 absorption is the cause of the negative pressure associated with SOM, atelectasis, and cholesteatoma. It is clear, however, that sniffing oil into the ME demonstrates a paradoxical ET patency and that sniffing can cause the negative ME pressure commonly found in ME disease.

SUMMARY

As many as 43% of ears intubated for SOM, ME atelectasis, and postoperative modified radical mastoidectomy and atticotomy for cholesteatoma, when tested in a clinical setting, demonstrated an ET that was abnormally patent to sniffing. This finding supports Magnuson's concept that sniffing and an abnormally patent ET are factors in the causation of decreased ME pressure and in many ME diseases reputed to be caused by ET obstruction. Furthermore, in the 673 diseased ears studied in this series, 33% to 43% had no evidence of ET obstruction when tested.

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Ann Otol Rhinol Laryngol 97:1988

CARBON DIOXIDE LASER SURGERY IN OTORHINOLARYNGOLOGY: PULSED BEAM VERSUS CONTINUOUS WAVE BEAM

RUDOLF GROSSENBACHER, MD RUDOLF SUTTER, MD

ST GALLEN, SWITZERLAND

According to various authors, the use of the carbon dioxide laser beam in pulsed form has the following advantages: better cutting action at the same mean power as that of the continuous laser, and less tissue damage at the edge of the cut. To date, however, there are no conclusive tests that demonstrate that pulsed operation of the CO_2 laser has clear advantages over continuous operation. This study compares the effects of a pulsed laser and a continuous laser on freshly removed human palatine tonsils and skeletal muscle tissue. The depth of thermal tissue damage was measured microscopically. It was observed that the depth of damage at the edge of the cut tissue decreased with increasing power density with both the pulsed laser and the continuous laser. With comparable power densities, however, pulsed operation unexpectedly produced somewhat deeper damage at the edge of the cut than did the continuous operation. The results obtained indicate that the pulsed CO_2 lasers available today have no advantages over the continuous mode CO_2 lasers for otolaryngologic surgical applications.

KEY WORDS — carbon dioxide laser surgery, continuous mode, pulsed mode.

INTRODUCTION

Over the past few years, the carbon dioxide laser beam has become increasingly important as a cutting tool in various surgical fields. Because of its energy absorption characteristics, which are pigment-independent, a precise control of its effects in the tissue is possible. It is therefore particularly suitable for operations in the upper aerodigestive tract.[1-4]

The cutting and hemostatic properties of the continuous CO_2 laser beam were discovered by Yahr and Strully[5] in 1966. In 1968, Hill[6] described a new type of laser, the rapid super-pulsed CO_2 laser. Continuous lasers have a constant output over a period of time. In contrast, pulsed lasers emit their beams in short pulses with high peaks, each of which is separated from the others by an emission-free interval (Fig 1). While the effect of the continuous CO_2 laser has been tested extensively experimentally and clinically, little is known about the effect of the pulsed CO_2 laser on tissue. In the opinion of various authors,[7-9] changing the continuous energy profile into a pulsed one not only gives a better cutting effect for the same mean power but also produces less damage to the adjacent tissue. There are today no relevant experimental investigations that demonstrate an advantage to using the pulsed CO_2 laser in the upper aerodigestive tract. Obvious questions must be asked about the relative effectiveness of each mode of laser application:

1. What is the relationship, for continuous and pulsed operation, between the effective energy density and the depth of damage at the edge of the cut?
2. Does the pulsed CO_2 laser beam produce a better cutting effect than the continuous one for comparable energy densities?
3. Is the damage adjacent to the cut less deep for the pulsed CO_2 laser than for the continuous one with comparable energy densities?

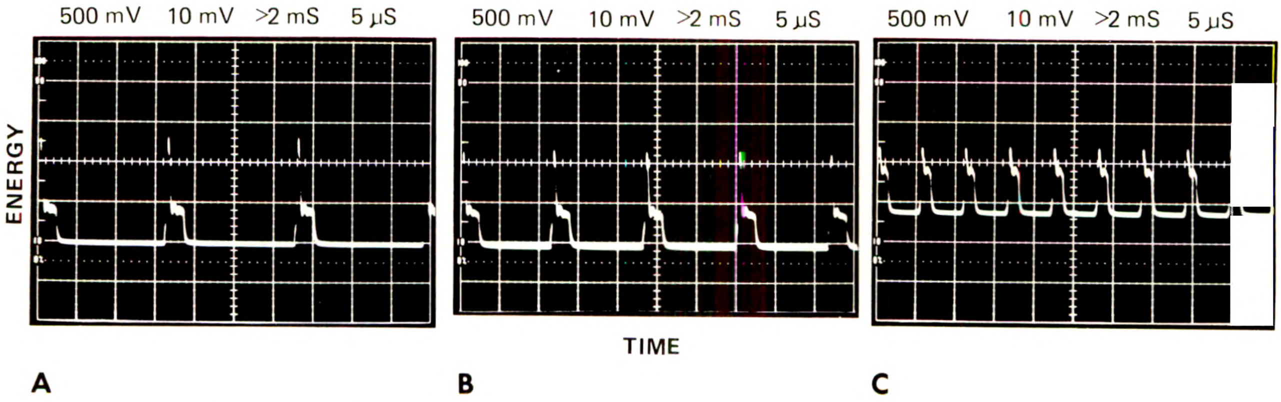

Fig 1. Carbon dioxide laser pulses at different repetition rates. A) 230 pulses/s, B) 320 pulses/s, C) 600 pulses/s.

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REPRINTS — PD Dr R. Grossenbacher, Dept of Otorhinolaryngology, Head and Neck Surgery, Kantonsspital, CH-9007 St Gallen, Switzerland.

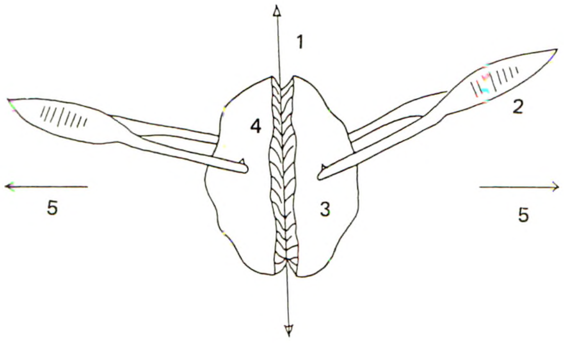


Fig 2. Tonsil incision in longitudinal direction. 1 — movement of laser beam, 2 — forceps, 3 — tonsil, 4 — incision being made, 5 — direction of pull.

By using a commercially available CO_2 laser apparatus (continuous and pulsed operation) on freshly removed human palatine tonsils and human skeletal muscle, we attempted to answer these questions.

MATERIAL AND METHODS

The CO_2 laser apparatus used was the model 250 Z surgical CO_2 laser system (Cooper, Santa Clara, Calif). This apparatus permits both continuous and pulsed operation (pulse parameters: 250 W peak power, 0.1- to 0.9-ms pulse duration, 10 to 990 pulses/s). For the experiments, the laser apparatus was coupled to an operating microscope (Zeiss Op Mi 1). The test tissue used comprised 58 freshly removed palatine tonsils and a sternocleidomastoid muscle that had been removed in a radical neck dissection. Directly after removal, the tonsils and the skeletal muscle were cut through surgically with a CO_2 laser using various parameters, at a working distance of 400 mm and with the smallest possible focal diameter (1 mm) (Fig 2). The cutting effect was assessed always by the same author immediately after each cut and recorded on the basis of the following scale:

1. Poor cut quality (minor carbonization without clearly visible cutting effect by moving the laser beam over the tissue surface);
2. Inadequate cut quality (minimal cutting effect visible by moving the laser beam over the tissue surface);
3. Average cut quality (clear cutting effect but no dehiscence of the wound by moving the laser beam over the tissue surface);
4. Good cut quality (slight dehiscence of the wound by moving the laser beam over the tissue surface); and
5. Very good cut quality (clear dehiscence of the wound by moving the laser beam over the tissue surface).

After fixation of the processed tissue in 4% formalin solution and embedding in paraffin, it was stained with hematoxylin and eosin. The depth of visible damage from the cut edge in the preparation was measured under a magnification of x320 using calibrated cross hairs on the lens of the microscope. All measurements were carried out by the same author, who at the time of measurement was not aware of the laser parameters used for the preparation. Since the depth of damage to tonsil tissue can vary from place to place even with the same laser parameters, 25 measurements in randomly selected areas were carried out for each specimen (Fig 3), and the mean value and standard deviation were calculated.

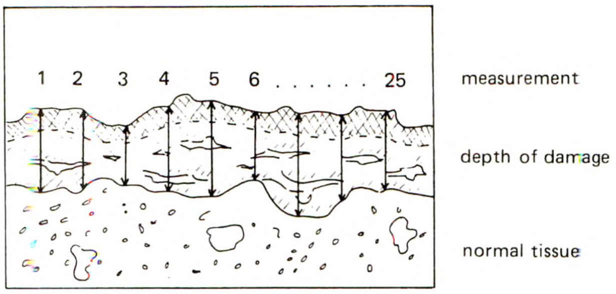


Fig 3. Determination of depth of damage by 25 measurements in randomly selected areas.

In the investigations to compare the action of continuous and pulsed CO_2 laser beams on the tissue, the mean power of the CO_2 laser beam at the site of action was recorded from calorimetric measurements. The apparatus used for the measurements was laser power probe model 25-A (Optical Engineering, Santa Rosa, Calif).

RESULTS

TONSILLAR TISSUE

Histologic Morphology of Edge of Cut. Three layers can be distinguished histologically at the edge of the laser beam–produced cut in tonsillar tissue (Fig 4), although layer 3 is not well defined in all specimens. Layer 1, the carbonization zone, consists of yellowish-brown, fine grained, irregular material having a mottled black appearance in parts, and measures on average about 15 μm. Layer

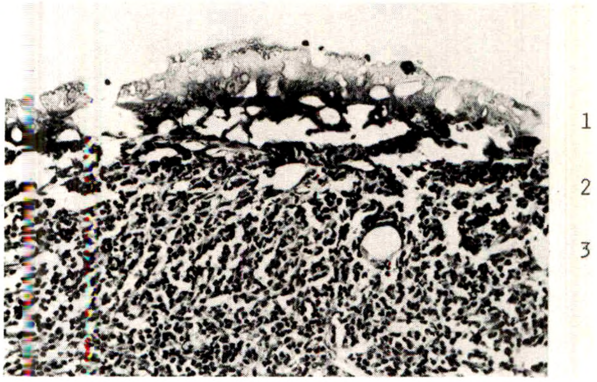


Fig 4. Histologic determination of three layers at edge of laser beam cut (H & E, original x200). 1 — carbonization zone, 2 — necrosis zone, 3 — edema zone.

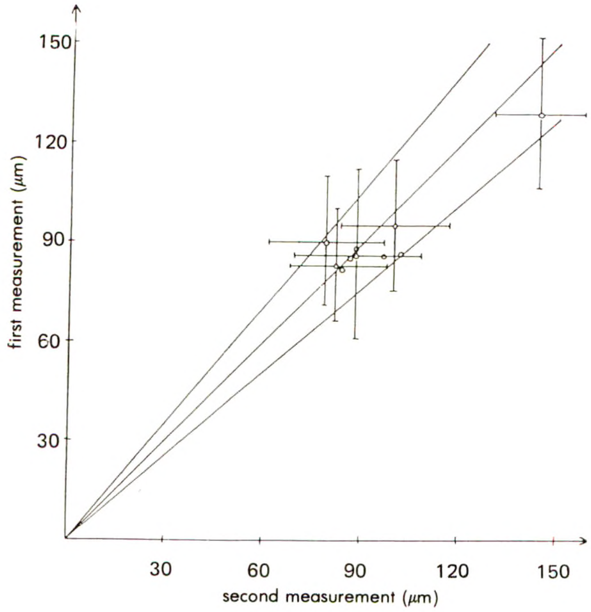


Fig 5. Reproducibility of repeated measurements of total depth of damage at cut edge. All values are in range ±15%. For clarity, standard deviations have been omitted for some mean values.

2, the necrosis zone, stands out as a dark reddish violet zone, 80 to 100 µm thick, even under low magnification. Cell clusters in the form of compact nets are located between more or less pronounced lacunae. In this area, the cell boundaries are difficult or impossible to detect. The cell nuclei are closely packed together and in areas are even fused together. Some of the nuclei have shrunk, or nuclear debris is observed. Layer 3, the edema zone, is not well separated from the normal tissue. The cell clusters in this third zone are somewhat looser, ie, the cells are somewhat further apart from one another. The histologic appearance of the tissue at the edge of the CO2 laser cut showed no fundamental difference in tonsils processed by the continuous and pulsed laser beams.

Reproducibility of Repeated Measurements of Depth of Damage. The depth of damage was measured repeatedly for ten tonsils cut using the general test setup (Fig 2) with various parameters. The test setup is intended to show whether it is possible to measure a reproducible depth of damage, given the fact that the boundary between normal tissue and the damaged tissue structure is sometimes difficult to determine. From the graphic comparison of the mean values for the depth of damage (Fig 5), it can be seen that all values are in the range of ±15%, which represents good reproducibility.

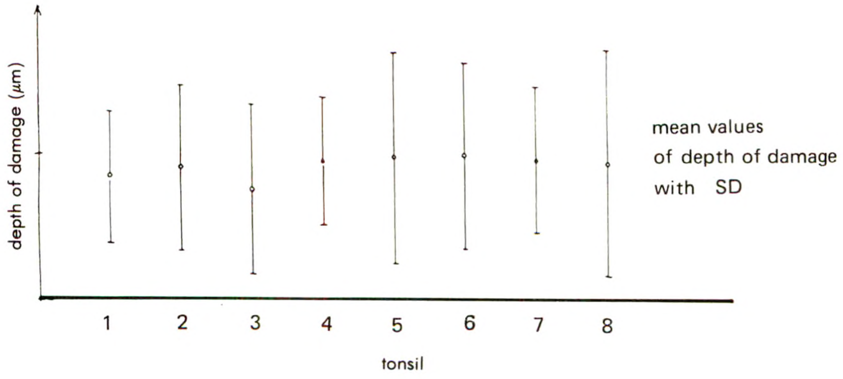
Interindividual Differences in Measurement of Depth of Damage for Same Output. Eight tonsils from four patients were cut through using the general test setup (Fig 2), an output of 25 W in each case, and continuous operation. The test setup is intended to show whether the same depth of damage is found with the same laser parameters for tonsils from different patients. It was found that, despite substantial differences in the ages of the patients from whom the tonsils had been taken, no significant difference in the depth of damage at the cut edge was observed, as can be seen from the plot of the measured values (Fig 6).

Cut Quality and Depth of Damage. First, 24 tonsils were cut through by continuous operation and 24 tonsils were cut through by pulsed operation, the general test setup (Fig 2) being used with various outputs (10 to 35 W). The cut quality was recorded immediately after each cut, in accordance with the scale described above, and the depth of tissue damage was measured at the cut edge after histologic processing. This test setup gives information about the effect of the CO2 laser output and the power density on the cut quality and on the lateral depth of damage at the cut edge for continuous and pulsed operation. The results are shown in Figs 7 and 8.

Effect of Output on Cut Quality. The graph (Fig 7) shows that increasing the power leads to improved cut quality. No unambiguous difference between continuous and pulsed operation is found with regard to cut quality for the same output power or similar power density.

Effect of Power on Extent of Tissue Damage. For both continuous and pulsed operation of the CO2 laser, the depth of damage in the tissue adjacent to the cut edge is substantially smaller when higher outputs were used. This is shown in Fig 8. The regression lines illustrate the very significant decrease in the depth of damage, from 104 µm (continuous

Fig 6. Measured values for eight different tonsils cut through surgically with CO2 laser using same output (25 W, continuous).



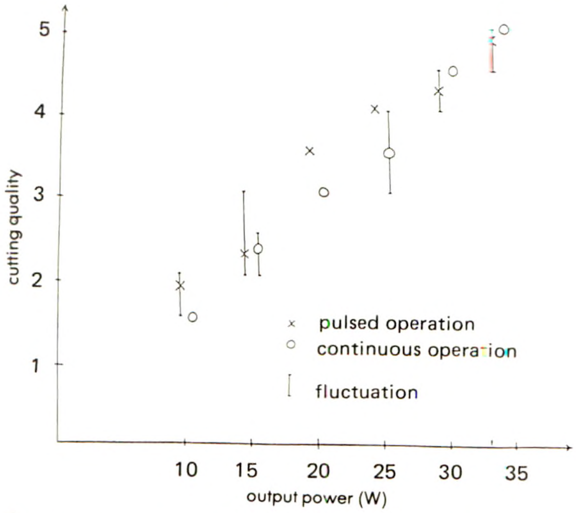


Fig 7. Effect of output power on cutting quality in tonsil tissue. 1 — poor, 2 — inadequate, 3 — average, 4 — good, 5 — very good.

operation) and 112 μm (pulsed operation) at 10 W (power in tissue) to, respectively, 79 μm (continuous operation) and 98 μm (pulsed operation) at 25 W (power in tissue).

Comparison of Depth of Damage From Continuous and Pulsed Laser. By means of calorimetric measurements, it was found that with the same output power, the laser beam power at the site of action is at least 10% lower in the case of pulsed operation than for continuous operation. The same applies to the power densities. Consequently, it is not strictly correct to make a direct comparison between the measurements of damage depth for continuous and pulsed operation with the same output power. It is possible, however, to compare the regression lines (described in the previous section) for all individual mean values of damage depth (based on power in the tissue), namely, those for continuous operation with those for pulsed operation (Fig 9A). The two regression lines lie close together at low power, but diverge at higher power (20 to 30 W power in the tissue). Here, the damage adjacent to the cut edge, in histologic terms, extends more deeply in the case of the pulsed CO_2 laser than for the continuous CO_2 laser; however, the scatters of the individual measured values about the regression lines are relatively large (see confidence hyperbolas, which include 95% of all expected values, Fig 9B). For lower powers, pronounced overlapping of these scatter ranges are observed; in the higher power range (above 15 W power in the tissue), they touch one another. Consequently, above 15 W, it is possible to discuss differences only in terms of trends, the differences being statistically nonsignificant. (The *t* test to compare the slopes of the regression lines indicates nonsignificance.)

SKELETAL MUSCLE

Comparison of Depth of Damage From Continuous and Pulsed Laser. A freshly removed human sternocleidomastoid muscle was cut through surgically eight times with a CO_2 laser, four times by continuous beam and four times by pulsed beam. For comparable power densities, the mean values of the depth of damage at the cut edge in the case of the pulsed beam were greater than the values for the continuous beam (Fig 10). Thus, in muscle there was also a detectable trend toward deeper tissue damage at the edge cut by the pulsed beam than at the edge cut by the continuous beam. The small number of observations does not permit any detailed statistical analysis.

DISCUSSION

Processing tonsil tissue and skeletal muscle tissue removed immediately after operation yields material from the otorhinolaryngologic area (mucous membrane, lymphocyte-rich stroma, and muscular tissue) that is representative and of use in answering the questions posed above. The disadvantage of working with tissue that already has been removed from the body is that the histologically defined symptoms of death (such as karyolysis, karyopyknosis, and karyorrhexis) and reactions of the environment to cellular death (such as edema and granulocyte reaction) are not detectable; a tissue that was still alive would be required for this purpose. However, even in tissues that have already been removed, the depth of damage at the edge cut with a CO_2 laser beam can be judged. This was shown by Grossenbacher[3] in 1985 by means of enzyme-histochemical investigations using dogs' tongues. Furthermore, in this experiment it was not the absolute depth of damage at the cut edge that was of primary importance, but rather a comparison of the damage from continuous and pulsed CO_2 laser operation. This comparison was possible using the depth of damage that was histologically clearly visible in tissue that already had been removed from the body.

A precondition of the comparative investigations into tonsil tissue is the experiment that demonstrates the reproducibility of the method of measurement and shows that there is no significant interindividual tissue effect on the depth of damage at the cut edge (Figs 5 and 6). The considerable fluctuations in the measured depth may have the following causes:

1. Different tissue structures (tonsils with a greater or lesser amount of connective tissue);
2. Cut edge phenomena due to the method of preparation;
3. Tangential damage zone in the preparation;
4. Unclear boundary in places between normal and pathologic tissue;
5. Forceps exerting different forces while pulling during cutting; and
6. Fluctuations in focus.

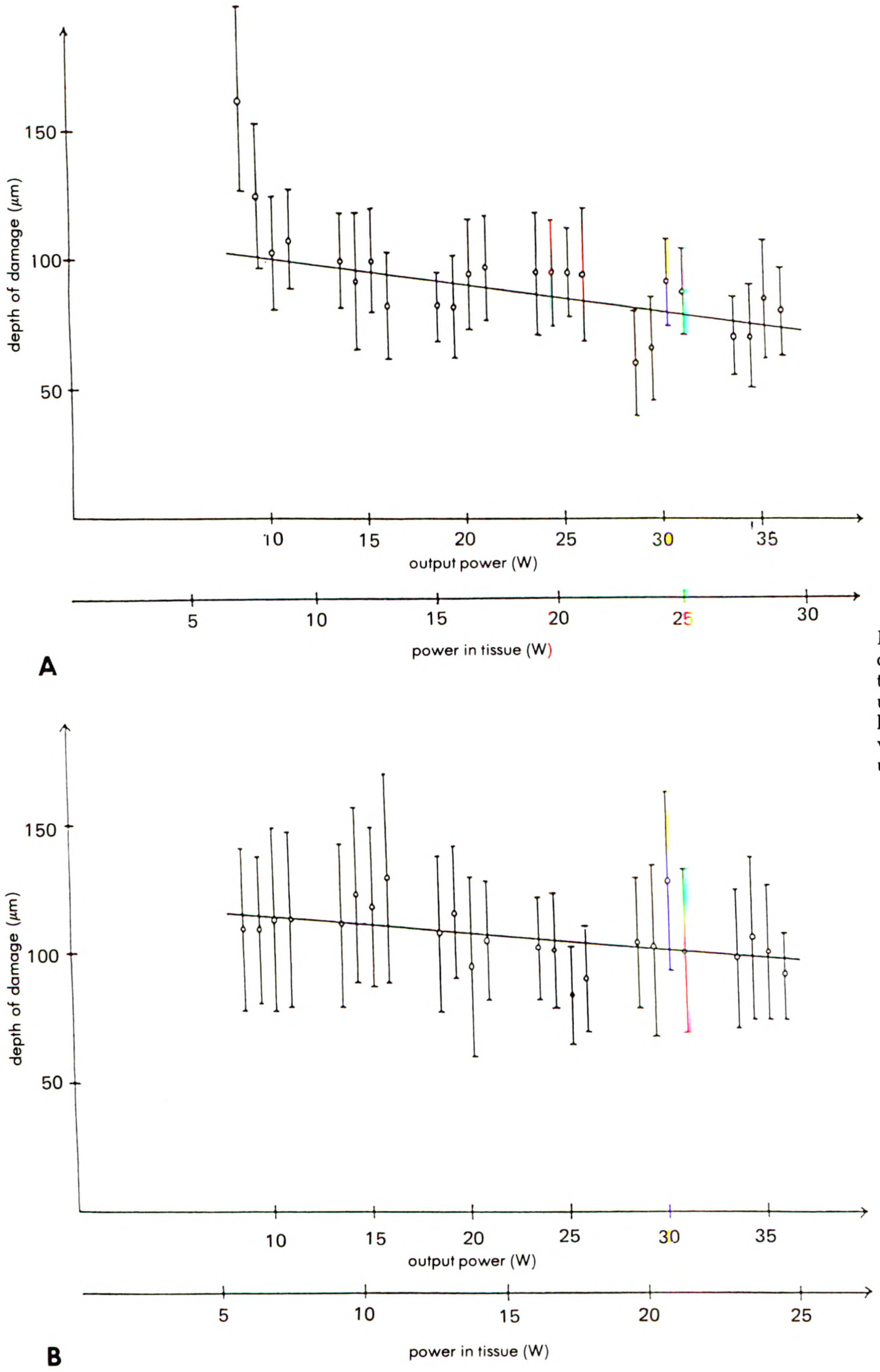


Fig 8. Total depth of damage at cut edge of 24 tonsils that were cut through surgically with CO2 laser using various powers. Regression lines drawn fall off significantly with increasing power. A) Continuous mode. B) Pulsed mode.

The parameters mentioned, which affect the test results, also play a role in every practical surgical application of the CO2 laser beam in the patient. Consequently, with regard to the questions posed in the present work, it is not at all necessary or desirable for the above factors to be excluded.

Apart from the focal diameter and the speed of movement of the laser beam, the output of the CO2 laser directly affects the cutting quality of the CO2 laser beam. The cutting quality is better the higher the output selected, regardless of whether continuous or pulsed operation is chosen (Fig 7). It is clear that the test setup gives a subjective assessment of cutting quality.

In both pulsed operation and continuous operation, the output selected has a significant effect on the depth of damage at the edge cut with the CO2 laser beam (Fig 8). There is a significant trend to-

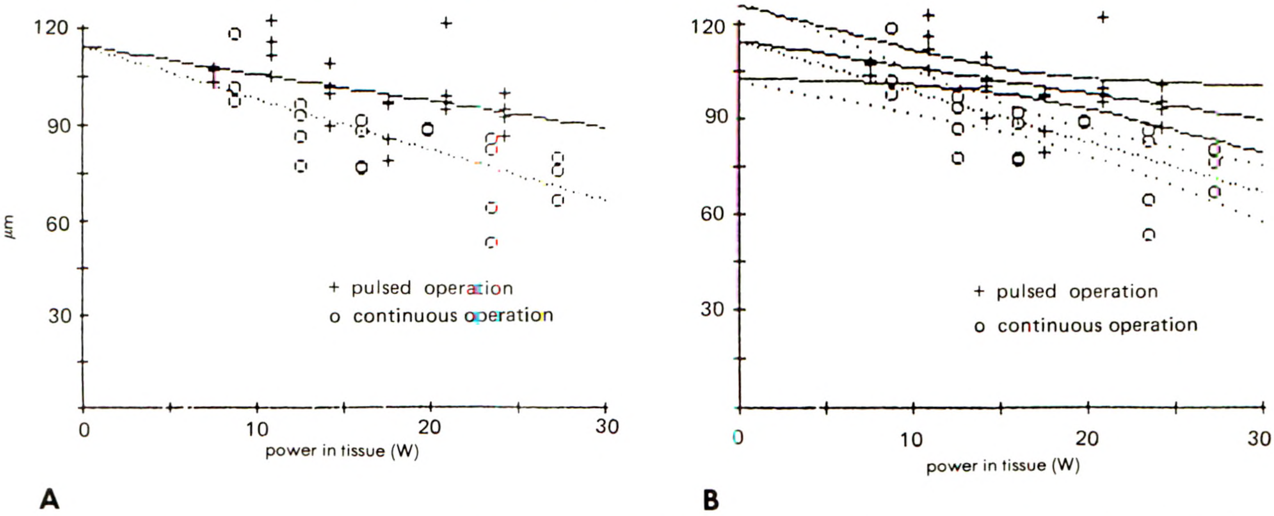


Fig 9. Comparisons of regression lines of all individual mean values of damage depth in A) regression lines alone, and B) with plot of confidence hyperbolas, which include 95% of all expected values.

ward shallower damage at the cut edge at higher powers. This can be explained in terms of the shorter time of action at the same point owing to the stronger and faster cutting achieved at high power.

The results obtained — namely, better cutting quality and less damage to the tissue at the edge of the cut with higher power densities — led to the conclusion that it is advantageous to use as high an output as possible, provided that the direct depth effect can be controlled adequately.

The most informative part of the entire study, however, was the comparison of the depth of tissue damage at the cut edge for continuous operation on the one hand and pulsed operation on the other. Contrary to expectations, there was a trend, both with tonsil tissue and with skeletal muscle tissue, toward a deeper damage zone at the cut edge in the case of pulsed operation (Figs 9A and 10), although the trend was not significant.

These results give rise to the question whether, in pulsed operation, it is possible to achieve the theoretic concept of tissue protection at the cut edge by recovery of the tissue during the pulse-free interval. The tests showed that pulsed operation has no advantage over continuous operation in tonsil and skeletal muscle tissue. Virtually the same cutting quality was obtained at all selected outputs.

Based on these observations, to date we do not use the pulsed CO_2 laser for patient care. This is not to say that the pulsed CO_2 laser beam has no future application in medicine. It is quite easy to imagine that a different type of tissue (eg, brain or liver tissue) may react completely differently to pulsed CO_2 laser energy. From a purely theoretic point of view, a pulsed CO_2 laser beam with a significantly shorter pulse duration (microsecond or even nanosecond range), with individual high-energy pulses and with a fairly long recovery time (long pulse interval) could result in less damage at the cut edge. This has been demonstrated for laser beams of other wavelengths.[8,10] Whether such a pulsed CO_2 laser beam with individual high-energy pulses would be sufficiently controllable as to depth and also have an adequate hemostatic effect, which is very desirable in laryngeal surgery in particular, will have to be demonstrated by the development of new laser systems and further experiments. In this respect, intensive cooperation between physicists, engineers, and members of the medical profession is very important.

CONCLUSIONS

The following conclusions can be drawn from our results:

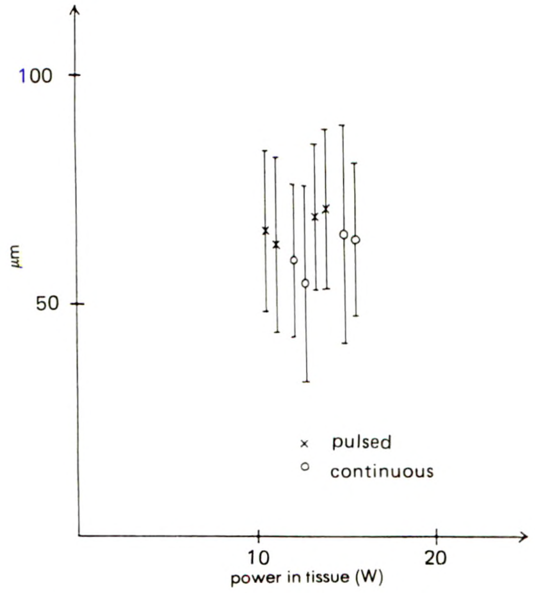


Fig 10. Comparison of histologically detectable depth of damage at cut edge in skeletal muscle with use of continuous and pulsed CO_2 lasers. Trend is toward deeper tissue damage with pulsed operation.

1. When freshly removed human palatine tonsils are cut with CO_2 lasers, the depth of damage at the cut edge decreases significantly with increasing output and power density, both in continuous operation and in pulsed operation.
2. The cutting quality for the tonsil tissue improves as the output power is increased, regardless of whether continuous or pulsed operation is selected.
3. Contrary to expectations, in both tonsil and the muscle tissue, pulsed CO_2 laser incision causes deeper damage at the cut edge than continuous CO_2 laser incision does, although the difference is not significant.

The results show that, in otorhinolaryngology, currently available pulsed CO_2 lasers have no advantages over continuous CO_2 lasers in their effect on tissues. Furthermore, it is advantageous to employ high outputs to achieve a good cutting quality and minimal injury to adjacent tissues.

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FACIAL MUSCLE REINNERVATION: A COMPARISON OF NEUROMUSCULAR PEDICLE WITH DIRECT NERVE IMPLANT

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Two methods of reinnervation, the neuromuscular pedicle (NMP) and the nerve implant (NI), were compared in a model using the rabbit's denervated mentalis muscle. Results from evoked electromyographic (EMG) and muscle tension studies (twitch and tetanic contraction) provided the basis of comparison. In addition, the timing of denervation was studied (ie, at the time of implantation of the NMP or NI, or 2 weeks following implantation). The NMP achieved more rapid reinnervation and produced stronger contractions than the NI. Demonstrable reinnervation with an NMP was accelerated when the implantation occurred prior to the denervation. This was not the case with the NI. There was poor correlation between the evoked EMG potential and the strength of both twitch and tetanic contraction. It was concluded on the basis of this study that muscle tension provided a more accurate means of assessing reinnervated muscle function. Of the two methods, the NMP would seem, therefore, to be the technique of choice when it is available. The NI is certainly effective and should be used when a satisfactory NMP is not available.

KEY WORDS — nerve implant, neuromuscular pedicle, reinnervation.

INTRODUCTION

Rehabilitation of the paralyzed face remains a formidable problem. Many different techniques are available to the surgeon,[1] and rarely, including in primary neurorrhaphy, are all the criteria for success fulfilled. The ideal result combines normal symmetry at rest with symmetric voluntary and mimetic movement without synkinesis or loss of adjacent nerve function.[2] Reinnervation with a neuromuscular pedicle (NMP) or a nerve implant (NI) offers a potentially successful approach to this problem. These methods do not exclude the possibility of spontaneous recovery (A. F. Inglis, R. E. Trachy, C. W. Cummings; unpublished observations), thus allowing early intervention before the muscle atrophies or becomes fibrosed. Theoretically, at least, this technique enhances the patient's prognosis.

Tucker et al[3] used the NMP for laryngeal reinnervation and later applied this technique to the paralyzed face, first in animals[4] and then in humans.[2] The results of both laryngeal and facial reinnervation have been variable. Tucker's own results are excellent,[2,5] but others[6] have abandoned the procedure as useless. The Seattle experience in facial reinnervation (using the NMP) has been encouraging,[7] and this has stimulated us to further research. One must remember that the often excellent results from animal experimentation are not always replicated in humans, and thus the findings of any project should not be overinterpreted.

Early research on reinnervation employed NIs, but with the development of the NMP, some investigators have adopted this as the method of choice. Doyle et al[8] used recurrent laryngeal NIs to reinnervate posterior cricoarytenoid muscles, and Crumley[9] has similarly used a phrenic NI. Meikle et al[10] compared the NMP with the NI in denervated cervical strap muscles and found that both methods reinnervated paralyzed muscles, but that the NMP was marginally more successful.

One model (A. F. Inglis, R. E. Trachy, C. W. Cummings; unpublished observations) used the rabbit's mentalis muscle to assess facial reinnervation. This muscle has the advantage of being subcutaneous, easily accessible, and supplied by a single nerve. Reinnervation with an NMP was demonstrated successfully, as well as dual innervation with recovery of the host nerve. Using this model, we have compared the results of reinnervation using an NMP with those from a direct NI. We have tried to assess the optimal time to perform a reinnervation, as well as to compare and correlate the various methods of measuring function.

METHOD

Twelve adult male New Zealand white rabbits (*Oryctolagus caniculus*) of similar size were used in this study. Three were allocated to each of four groups: 1) group A — mentalis muscle reinnervation performed 2 weeks after denervation, 2) group B — mentalis muscle denervation and reinnervation carried out sequentially in the same procedure, 3) group C — denervation 2 weeks after mentalis muscle reinnervation, and 4) group D — reinnervation without a denervation procedure. In all rabbits, one mentalis muscle was reinnervated with an NMP and the other with an NI. No attempt was made to randomize the sides. Following reinnervation, the rabbits were stimulated transcutaneously (under anesthesia) at approximately twice-weekly intervals

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using a Hilger nerve stimulator, and the date of the first reinnervation twitch was recorded. Animals in group C were stimulated every 1 to 2 days following denervation, again until reinnervation was evident.

Operative Technique. Anesthesia was induced and maintained by intramuscular ketamine hydrochloride (35 mg/kg) and xylazine (5 mg/kg). A 1.5- to 2-cm segment of facial nerve was excised after dissecting it back to the stylomastoid foramen. The neck was explored through a midline incision from mandible to sternum, avoiding damage to the mentalis muscles. These originate on the mandible and insert into the skin around the lower lip. Each ansa hypoglossus was identified, and a suitably long branch was traced to the point at which it penetrated muscle and arborized. On one side, the arborized nerve ending in a 2-mm cube of muscle (the NMP) was excised, while on the other the nerve was incised as it entered the muscle (the NI). The NMP was transferred up to the ipsilateral mentalis muscle and sutured in place with four 10-0 silk sutures. The NI was inserted into the other mentalis muscle after separation of a few superficial fibers and sutured in place with one 10-0 suture through the nerve sheath. Usually at least one submandibular gland was excised to reduce tension on the NMP or NI.

The terminal experiment was carried out 12 weeks after reinnervation. While the rabbit was still awake we looked for lip movements, either spontaneous or related to respiration. The animal was then anesthetized as before. Percutaneous hook electromyography (EMG) electrodes (Teflon-coated stainless steel 0.07 mm diameter, bared at the tip) were inserted into both mentalis muscles via 25-gauge needles. The EMG was amplified (Data Inc 2140 model 2) and continuously displayed on an oscilloscope (Tektronix type 565). Continuous EMG and respiratory movements (via a linear variable differential transducer) were recorded simultaneously on a Gould Brush recorder (type E-100D model 220). Recordings were made during quiet respiration, forced respiration (nasal obstruction), and increased nonforced respiration (breathing 100% nitrogen through a face mask).

Through a midline neck incision, the transferred ansa hypoglossi nerves were identified and mobilized. Stimulating electrodes (same wire as for EMG) were attached to a constant current stimulus isolator (BAK BSI-2) triggered by a Grass stimulator (model SD9). The evoked EMGs (eEMGs) were captured and analyzed on a Nicolet signal averager (model NTE 1170). The stimulus threshold and the minimum stimulus giving a maximal response were identified. This maximal response was recorded, and the latency, amplitude, and area under the curve were measured.

The EMG electrodes were removed, and the mentalis muscle insertion was dissected from the lip skin. The muscle was mobilized, and proximally the neurovascular bundle was preserved. An attempt was made to stimulate the host nerve. A 2-0 silk nooselike suture was placed around the distal end of the muscle and connected to a linear force transducer (Stratham DSC), a signal amplifier, and the Nicolet signal averager. Maximal twitch responses (stimulus as before) and tetanic responses (stimulus, 1.5 times maximal twitch stimulus; rate, 200/s; duration, 0.01 ms held for 1 to 2 seconds) were recorded and measured. The transducer was calibrated later using gram weights.

In group D, the facial nerve branch to the mentalis muscle was identified on the cheek and used for electrical stimulation. In addition, NI and NMP were identified and stimulated to ascertain if dual innervation had developed.

RESULTS

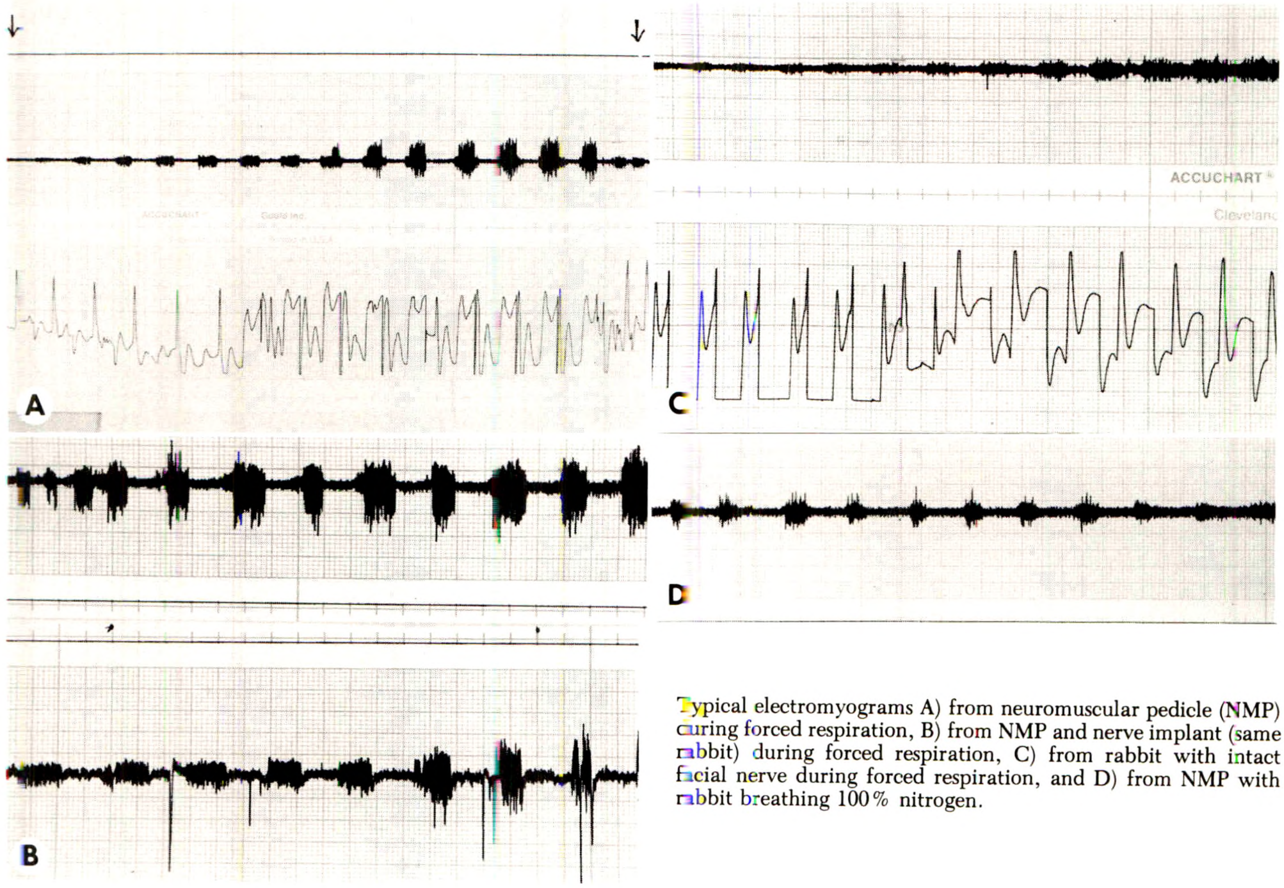
Reinnervation as determined by transcutaneous stimulation was successful in all rabbits in which the facial nerve was divided. No rabbit in groups A, B, or C had any spontaneous movement, but there was some electrical activity unrelated to inspiration. In group D, there were very infrequent lower lip movements (these were always much smaller than the constant nose wiggle also present) and more EMG activity.

Nasal obstruction led to an increase in EMG activity on both sides, and this increased as the accessory muscles of inspiration were used more and more forcefully. This was most dramatic in groups A, B, and C, but was also present in group D (see Figure, A-C). This increased EMG activity was easily visible as rhythmic contractions of the lower lip. It was usually possible to guess the side of the NMP as it gave a stronger contraction. In group D, there was a generalized facial muscle contraction with each inspiration.

When the rabbit was forced to breathe 100% nitrogen (to increase respiratory rate without altering airway resistance) there was a slower but definite increase in EMG activity, leading to lip movements as before (see Figure, D). There was no increase in group D.

In groups A, B, and C, reinnervation in all animals was first evident with the NMP (Table 1). Stimulation of the host (transected) nerve in groups A, B, and C, or the ansa hypoglossus in group D, did not cause a twitch, nor could an eEMG be captured.

On eEMG, there was marked interanimal and interside variation in both the size of response and thresholds (Table 2). The maximal response was defined as the minimal stimulating current that gave the largest amplitude; a further increase in stimulus led to a submaximal response. The ampli-



Typical electromyograms A) from neuromuscular pedicle (NMP) during forced respiration, B) from NMP and nerve implant (same rabbit) during forced respiration, C) from rabbit with intact facial nerve during forced respiration, and D) from NMP with rabbit breathing 100% nitrogen.

tude of the largest positive or negative wave was measured, as was the area under this peak.

Regarding force-tension measurement, in all animals there was a stronger response on the NMP side, both with the twitch (p = .004, paired *t* test) and the tetanic response (p = .007; Table 3). There was very little difference in weights between groups at termination, so this variable may be excluded.

DISCUSSION

The speed of reinnervation and high success rate endorse the usefulness of the rabbit mentalis muscle in this type of research. Reinnervation did not lead to any random lower lip movements. Normally these are infrequent, and always much smaller than the rabbit's constant nose wiggle. There was also less background electrical activity in all reinnervated muscles as compared with the normally innervated muscles. Visible submental contractions, coordinated with inspiration, were induced by obstructing the airway. This was not present (nor was there any increase in electrical activity) during normal respiration. Johnson and Tucker,[4] reinnervating the zygomatic muscle, found the rabbit's constant nose wiggle returned within 5 to 26 days. This suggests that the muscle is dominant over the nerve. Our work suggests, as have other studies[11] previously, that the nerve is dominant, ie, the reinnervated muscle should develop the function of a strap muscle and move with inspiration.

Comparison of Function. The results of this study suggest that the NMP is superior to the NI in two ways: 1) shorter time to demonstrable reinnervation and 2) more forceful responses to twitch and tetanic stimulation. However, one should note that it may be disadvantageous to have overly strong responses, especially in the face. What is desirable is good tone without synkinesis.

It may be that the strength of the implanted muscle would have increased had we delayed the termination date.

Reinnervation was fastest on the side of the NMP in all animals. Tucker and Ogura[12] originally thought that the NMP acted by implanting reinnervated motor end-plates. More likely, the NMP acts

TABLE 1. RETURN OF FUNCTION

Group	*Method*	*Time of First Movement*	*Average*
A	NMP	2.5, 2.0, 2.5 wk	2.3 wk*
	NI	5.0, 3.0, 3.0 wk	3.7 wk*
B	NMP	2.0, 2.5, 3.0 wk	2.5 wk*
	NI	6.0, 4.5, 4.5 wk	5.0 wk*
C	NMP	6.0, 5.0, 7.0 d	6.0 d†
	NI	4.0, 6.0, 4.0 wk	4.7 wk†
D	NMP	No movement	—
	NI		

*Timed from date of reinnervation.

†Timed from date of facial nerve division.

TABLE 2. GROUP-AVERAGED ELECTROMYOGRAPHY

Group	*Method*	*Threshold (μA)*	*Maximum Response (μA)*	*Amplitude Maximum Response (mV)*	*Area Under Curve**
A	NMP	51	597	1.6	441
	NI	132	593	0.9	247
B	NMP	151	250	1.0	284
	NI	288	427	0.4	127
C	NMP	161	537	1.0	270
	NI	108	283	0.8	204
D	Stimulated via facial nerve	168	593	1.6	414

*Units are difference between cursors on Nicolet signal averager.

as a donor for multiple NIs. This could speed up reinnervation, as some of these nerves would not be divided and hence would not undergo wallerian degeneration before sprouting occurred.[13] Aguilar et al[14] have confirmed that sprouting is dependent on axoplasmic flow. Crumley[15] believes that the NMP leads to local fibrosis and that this could obstruct the sprouting nerve. This would appear not to have a detrimental effect — possibly many nerve fibrils have crossed this interface before fibrosis occurs. Indeed, this is likely if our understanding of the function of the NMP is correct.

Timing of Reinnervation Surgery. Our numbers and differences do not allow us to draw any conclusions about the timing of reinnervation. We feel that timing is unlikely to be of any major clinical significance, provided the surgery is not delayed too long. Tucker[5] has reinnervated larynges successfully after 50 and 22 years. Some histologic evidence in human facial muscles after 36 years[16] suggests that at least some return of function is possible. Undoubtedly, an earlier procedure with less time for atrophy and fibrosis would be desirable.

Reinnervation, or dual innervation, is not possible unless denervation occurs at least temporarily.[17] Fex and Thesleff,[18] using a tibial NI into the gastrocnemius muscle in rats, described an increased speed of reinnervation if the reinnervation procedure occurred before denervation. They found that sequential denervation and reinnervation led to a stimulatable response in some rats after 12 days, while with denervation delayed by 2 or 12 weeks, a response was present as early as 2 days. They also found that delaying the reinnervation procedure led to a stronger contraction (confirmed in this study); this finding suggests reinnervation of more motor end-plates. We, and most researchers, found no response with stimulation while the host muscle was still innervated. Probably those who found a small response had accidentally denervated a few muscle fibers at the operation site.[17] We have confirmed Fex and Thesleff's work, but only with an NMP and not with an NI. Our results suggest that only the NMP sprouted prior to denervation, so possibly the muscle fibers in the NMP stimulated sprouting. This part of the experiment is worth repeating with larger numbers and different periods between reinnervation and denervation. Histologic evidence of sprouting from the NMP and NI before denervation also should be sought.

Hoffman[19] thought the stimulus for reinnervation was a so-called neurocletin coming from the damaged host nerve, and since then others have suggested similar agents.[9] Our group C results do not fit this hypothesis. Aguilar et al[14] thought the mechanism was more complex. They suggested that the target organ constantly made a stimulatory substance and that through negative feedback, sprouting was regulated by an inhibitory substance in the axoplasm of the intact innervation. Our results cast into doubt the existence of an inhibitory factor other than a local phenomenon preventing dual innervation without inhibiting sprouting.

Correlation Between eEMG and Function. Rosen and Jewett[20] suggest that the area under the curve is the most accurate method of assessing reinnervation. We measured correlation coefficients between our eEMG data (thresholds, maximal responses, amplitudes, and areas) and twitch and tetanic responses. The only significant ($p = .02$) correlation was between the area and tetanic contraction with the NMP. Our small numbers and variation made all the other correlations nonsignificant, although scatterplots suggested that a lower threshold, larger amplitude, or larger area under the curve correlated with increased function. The variation in our results makes us conclude that force-tension studies are the only accurate method of measuring function. Many reinnervation surgeons[21] agree that there is a poor correlation between EMG data and function.

TABLE 3. FORCE-TENSION MEASUREMENTS

Group	*Method*	*Maximum Twitch (g)*	*Tetanic Response (g)*	*Average Weight at Termination (kg)*
A	NMP	8.7	41	2.8
	NI	6.2	33	
B	NMP	9.7	44	2.6
	NI	6.3	36	
C	NMP	11.2	65	2.7
	NI	7.8	45	
D	Stimulated via facial nerve	9.3	40	2.8
All NMPs		9.9	50	
All NIs		6.8	38	

CONCLUSIONS

1. The rabbit mentalis muscle is a good model in which to study reinnervation techniques.
2. In terms of strength of contraction and speed of reinnervation, the NMP is superior to the NI.
3. Reinnervation with the NMP is accelerated if the reinnervation procedure precedes denervation.
4. Force-tension studies are the most accurate method of measuring function in reinnervated muscles.
5. While the NMP is best, the NI does give satisfactory reinnervation, and we suggest its use whenever a suitable NMP is not available.

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TECHNIQUE FOR EXTERNAL REPOSITIONING OF THE PARALYZED VOCAL CORD WITH SILASTIC IMPLANT

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A technique is introduced for vocal cord mobilization in which a tunnel is made through the inner perichondrium of the thyroid cartilage and a medical grade silicone is placed from the upper part of the thyroid cartilage and pulled out over the cricothyroid membrane. This technique was performed on six dogs, and results were compared to those of a modified laryngoplasty performed on another six dogs. The technique was refined on 20 cadavers and finally performed on five adult patients with more than 1 year of vocal cord paralysis. Results of this technique suggest that it constitutes a good alternative to Teflon injection; morbidity was minimal.

KEY WORDS — Silastic implant, vocal cord paralysis.

INTRODUCTION

Phonosurgery is a growing subspeciality in otolaryngology–head and neck surgery and involves a great number of applications, such as voice rehabilitation after ablative surgery of the larynx, management of the flaccid larynx, treatment for atrophy of the vocal cords, surgery for modification of vocal pitch, and treatment for vocal cord paralysis.

Until now, there have been several alternatives for the treatment of symptomatic vocal cord paralysis.[1-8] In 1915, Payr[9] used a tilted U-shaped incision on the thyroid ala to make a pedicled cartilage flap, which was depressed inward in order to shift the vocal cord medially. This constituted the first attempt at external mobilization of the vocal cord. In 1952, Meurman[10] used a cartilage implant taken from the costal rib and inserted between the thyroid cartilage (TC) and the inner perichondrium. In 1955, Opheim[11] used an incised segment of the TC, which was inserted into the inner perichondrium at the level of the vocal cord. This produced severe postoperative edema, which required tracheotomy. In 1968, Sawashima et al[12] inserted an incised segment of TC between the thyroid ala and inner perichondrium, with excellent results for the voice.

Isshiki et al[13,14] reported a thyroplasty for dysphonia due to vocal cord paralysis or atrophy as an alternative to intracordal Teflon injection, which is the most frequently performed procedure. Their technique consists of a rectangular incision over the thyroid ala, approximately 10 x 3 mm, the upper margin of which should be at the level of the vocal cord. A wedge of TC is inserted between the rectangular fragment and the remaining frame of the TC to enhance the compression effect on the vocal cord.

In 1986, Koufman[15] reported a modification of the medialization laryngoplasty of Isshiki et al that involves using a Silastic implant, which is custom fitted for each patient in order to obtain the best possible functional results. The present paper discusses Koufman's modified procedure and introduces another technique for vocal cord medialization, in which an incision over the external perichondrium of the medial upper part of the TC is performed and, as in a septoplasty, a tunnel is made through the inner perichondrium until the cricothyroid membrane is reached. A medical grade silicone is placed on the superior part of the TC and pulled out over the cricothyroid membrane. We report our results in dogs, cadaver specimens, and five patients, and compare this technique with Koufman's.

MATERIAL AND METHODS

Twelve adult mongrel dogs were used for the experiment. The dogs were divided into two groups. In the first experiment, five dogs were anesthesized with an intraperitoneal injection of pentobarbital sodium. After draping, shaving, and cleaning the neck, a vertical midline incision was performed in order to expose the larynx and left recurrent laryngeal nerve, which was sectioned, and a 2-cm sample of the nerve was taken after verifying normal vocal cord mobility through direct laryngoscopy.

The midline raphe of the strap muscles was incised, and these were reflected laterally, exposing the entire TC on the left side. The external perichondrium of the medial upper part of the TC was incised, and as in a septoplasty, a tunnel was made with the aid of a Freer dissector through the inner perichondrium until the cricothyroid membrane was reached. Here, a careful dissection was performed to avoid luxation of the cricothyroid joint and laceration of the mucosa in the subglottic region. Then a medical grade silicone in the form of a cylinder 4 mm in diameter, previously designed according to the cadaver larynx studies, was placed from the superior part of the TC and pulled out

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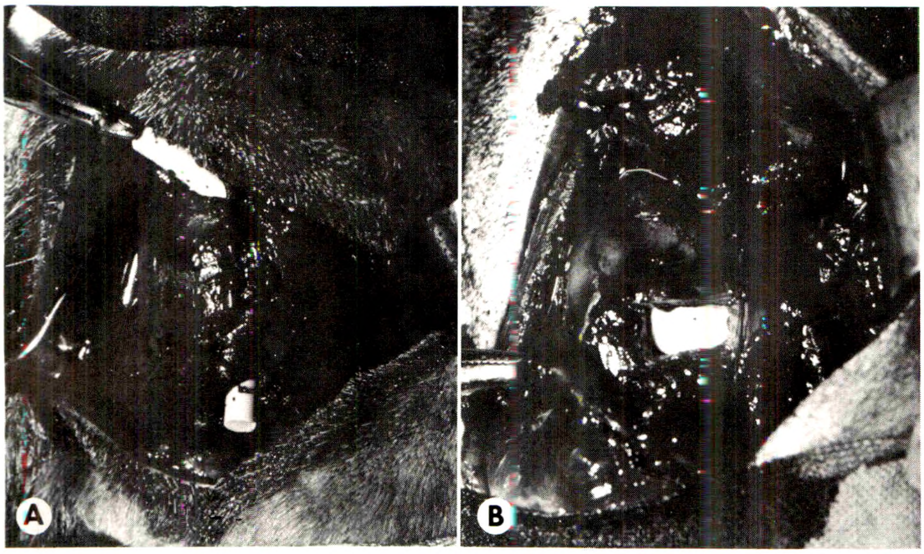

Fig 1. Photographs of cylindrical Silastic implants in dogs A) from upper part of thyroid cartilage to cricothyroid membrane (tunnel technique) and B) inside previously made window, over ala of thyroid cartilage.

over the cricothyroid membrane (Fig 1A). The Silastic was fixed with nonabsorbable sutures to prelaryngeal muscles. The wound was closed in layers. Perioperative antibiotics were administered to the animals.

The second experiment also was performed on five dogs. The preoperative procedures were basically the same, and the left recurrent laryngeal nerve was sectioned. In this group, Koufman's modification of the laryngoplasty devised by Isshiki et al was performed. A rectangular incision was made over the left thyroid ala according to Koufman's formula.[15] The upper margin of the incision was at the level of the vocal cord. The window of cartilage was cut with a No. 11 blade without perforating the inner perichondrium. A Cottle elevator was used to raise the inner perichondrium until the window of cartilage was free of the alar cartilage. Then a medical grade Silastic implant was positioned horizontally, pressing and medializing the cartilage window (Fig 1B). The wound was closed in layers.

The dogs were killed 1 week (two dogs), 2 weeks (two dogs), 3 weeks (two dogs), 6 weeks (two dogs), and 8 weeks (four dogs) postoperatively. Their larynges were removed, fixed in formalin, and stained with hematoxylin and eosin for light microscopic study.

In two additional dogs, one belonging to the first group and one to the second, the recurrent laryngeal nerve was not cut. Both were killed at 8 weeks postoperatively.

The dogs' barking was recorded on a cassette tape for evaluation before and after the operative procedure. The results were described as excellent (normal barking), good (nearly normal barking), and poor (dysphonia).

The second part of this study refers to the anatomic dimensions (Fig 2) of 20 adult human larynges (16 from males and four from females; age range, 20 to 64 years; mean, 30 years) from which the following mean measurements were obtained: 1) height of the central portion of the TC (20 mm); 2) height of the left thyroid ala (28.8 mm), 2A) height of the right thyroid ala (29.1 mm); 3) width of the left thyroid ala (36.3 mm), 3A) width of the right thyroid ala (36.4 mm); 4) distance between the true vocal cords and the inferior border of the TC (10.2 mm); 5) distance between the true vocal cords and the superior border of the TC (9.9 mm); 6) length of the vocal cords (20.2 mm); 7) distance between the posterior cricoid and the anterior commissure (30.2 mm); 8) height of the arytenoids (18.2 mm); 9) width of the interior larynx, taken from one external thyroarytenoid muscle to the other (19.6 mm); 10) width of the glottic lumen, with (4.2 mm) and without (7.0 mm) an implant; 11) width of the subglottic lumen, with (12.7 mm) and without (13.5 mm) an implant.

The surgical technique for external mobilization of the vocal cord was performed on all the larynges, and the glottic and subglottic lumens were measured with calipers before and after the introduction of the Silastic implant (4 mm). The larynges were fixed in formalin and stained with hematoxylin and eosin for light microscopic study (Fig 3A,B).

RESULTS

All the dogs tolerated the procedure well, and the fibrotic reaction around the silicone material was minimal (Fig 3C).

The group in which the tunnel technique was performed showed good compensation (lateralization) of the vocal cord. One dog developed a granuloma in the region of the anterior commissure. The barking recorded on a cassette tape showed excellent results (normal barking) in two dogs, good (slight loss of air) in two others, and poor (evident dysphonia) in one.

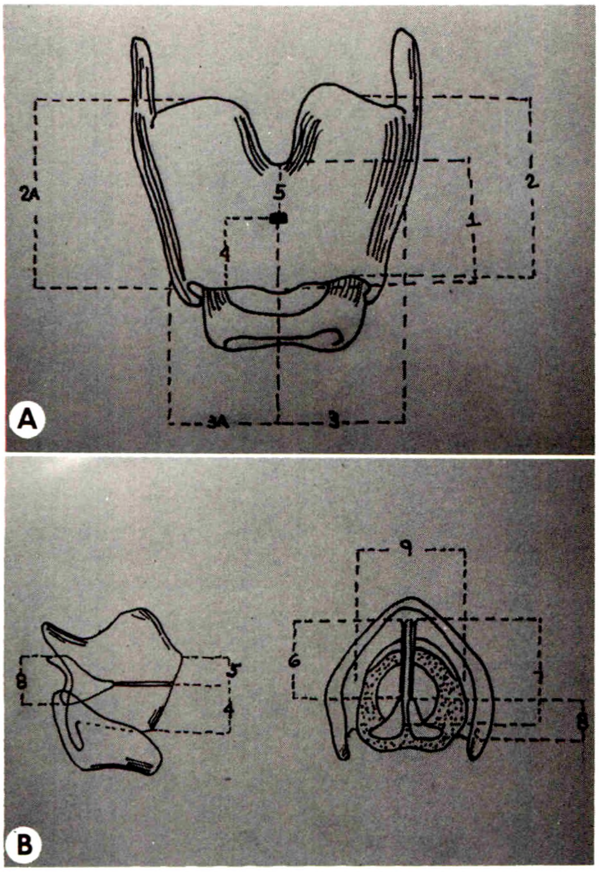

Fig 2. Views of larynx. A) Frontal view. 1 — height of central portion of thyroid cartilage (TC), 2 — height of left thyroid ala, 2A — height of right thyroid ala, 3 — width of left thyroid ala, 3A — width of right thyroid ala, 4 — distance between true vocal cords and inferior border of TC, 5 — distance between true vocal cords and superior border of TC. B) Lateral and coronal views. 4 — distance between true vocal cords and inferior border of TC, 5 — distance between true vocal cords and superior border of TC, 6 — length of vocal cords, 7 — distance between posterior cricoid and anterior commissure, 8 — height of arytenoids, 9 — width of interior larynx, taken from one external thyroarytenoid muscle to other.

In the second group, none of the dogs developed a granuloma. In one case, an abscess formed in the wound, compromising the results, and the prosthesis was removed. The implant was also well tolerated, with minimal reaction. Barking was excellent in two dogs, good in two, and poor in one (the one with the infection).

Concerning the two dogs in which the recurrent laryngeal nerve was not cut, one developed a granuloma of the anterior third of the medialized vocal cord.

The results of the anatomic measurements performed on the human larynges seem to indicate that the tunnel technique shortens the subglottic space, whereas the Koufman laryngoplasty does not. This effect did not seem to produce any functional deficit in the dogs, at least during the period of follow-up, and no diplophony was noticed.

It was evident that the thyroarytenoid muscles moved toward the midline after the introduction of the implants. This goal is reached in a similar way with both techniques.

CASE REPORTS

Case 1. A 27-year-old man had progressive idiopathic hoarseness, which had started when he was 13 years of age. A Teflon injection on the left vocal cord was performed when he was 20 years of age, with apparent early good results, but after several months the hoarseness became worse. When we first examined the patient, he had severe dysphonia, and indirect laryngoscopy revealed atrophy of the left vocal cord, which was lateralized. A direct laryngoscopy confirmed these findings. The vocal cord had an irregular shape and a stone-hard consistency. The patient did not have aspiration problems, and he was scheduled for vocal cord mobilization under local anesthesia via an external approach using Koufman's modification of the procedure of Isshiki et al. Several different sizes of Silastic implant were tried, and it was finally decided to leave two struts. The external perichondrium was used to seal the defect. The postoperative period was unremarkable and the patient's dysphonia improved, but a normal voice was not obtained. However, we consider this a successful procedure, because of the preoperative condition of the larynx.

Case 2. A 51-year-old woman underwent a section of the right recurrent laryngeal nerve after excision of a thyroid carcinoma. She developed a moderate dysphonia with minimal aspiration. Direct laryngoscopy showed a paramedian right vocal cord paralysis. A Koufman technique was performed, using the external thyroid perichondrium to seal the defect. She obtained a normal voice, but the aspiration was the same at her 10-month follow-up.

Case 3. A 60-year-old man developed an idiopathic left vocal cord paralysis with severe dysphonia and moderate aspiration. Direct laryngoscopy showed a lateralized left vocal cord. He underwent surgical medialization of the vocal cord with the tunnel technique, after which he obtained a nearly normal voice without aspiration on an 11-month follow-up (Fig 4A).

Case 4. A 70-year-old man developed severe dysphonia and aspiration after a cerebrovascular accident. Direct laryngoscopy revealed a lateralized left vocal cord paralysis. The tunnel surgical technique was performed, after which he obtained a nearly normal voice without aspiration on a 12-month follow-up.

Case 5. A 48-year-old woman developed aphonia and moderate aspiration secondary to lung carcinoma. Direct laryngoscopy revealed a paramedian left vocal cord paralysis. She underwent a tunnel

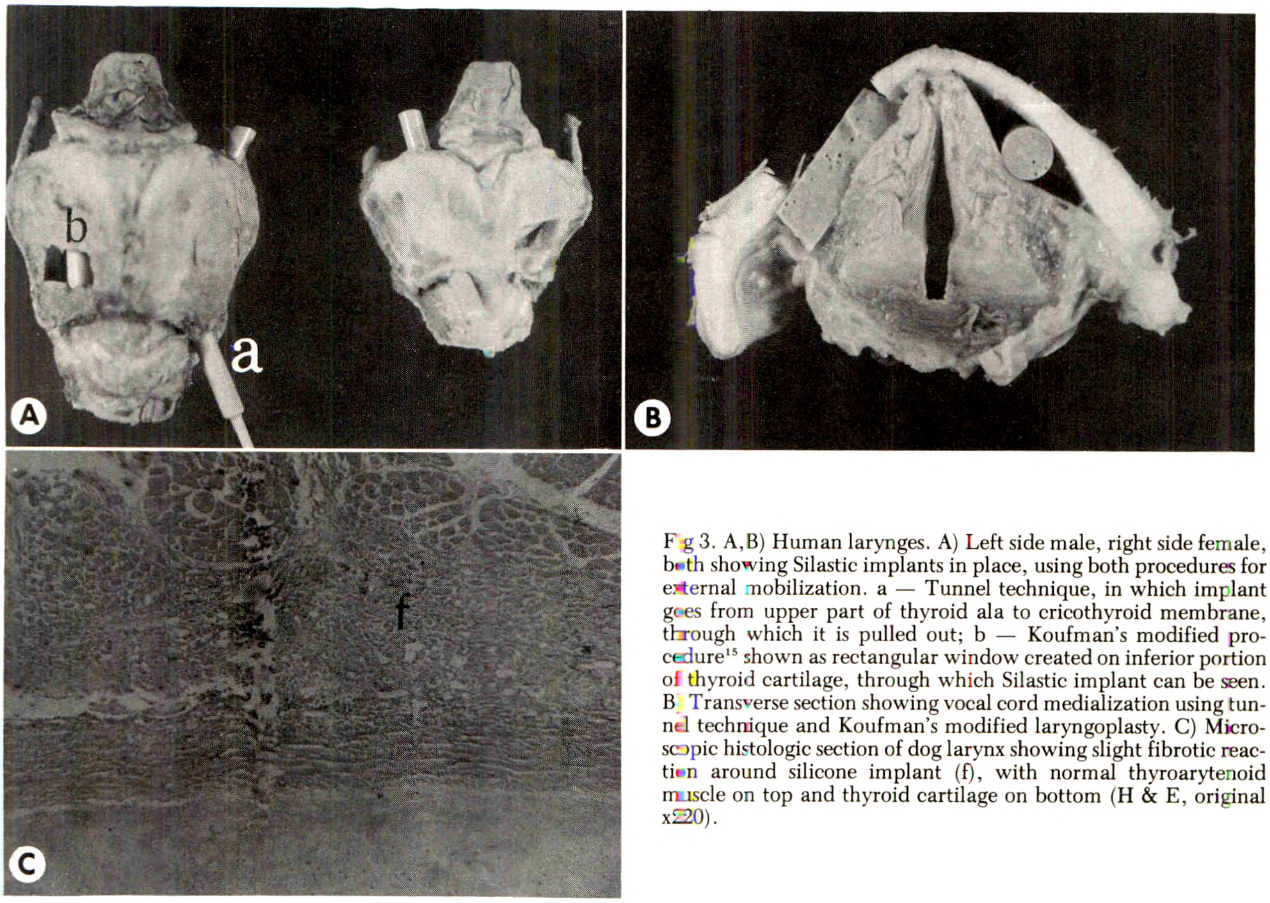

Fig 3. A,B) Human larynges. A) Left side male, right side female, both showing Silastic implants in place, using both procedures for external mobilization. a — Tunnel technique, in which implant goes from upper part of thyroid ala to cricothyroid membrane, through which it is pulled out; b — Koufman's modified procedure[15] shown as rectangular window created on inferior portion of thyroid cartilage, through which Silastic implant can be seen. B) Transverse section showing vocal cord medialization using tunnel technique and Koufman's modified laryngoplasty. C) Microscopic histologic section of dog larynx showing slight fibrotic reaction around silicone implant (f), with normal thyroarytenoid muscle on top and thyroid cartilage on bottom (H & E, original x220).

surgical technique for medialization of the vocal cord. Postoperatively she obtained a nearly normal voice, with minimal aspiration, which was the same on her 12-month follow-up.

DISCUSSION

Various techniques exist to alter vocal cord position surgically, with intracordal Teflon injection being the most popular.[16] However, as Koufman has pointed out, it has several disadvantages: 1) the need for patient cooperation under local topical anesthesia during direct laryngoscopy; 2) the need to be sure that motor function will not return to the injected vocal cord; and 3) the fact that the technique is not suggested in status postcordectomy, in the presence of atrophy and bowing of the vocal cord, or after laryngeal trauma causing a loss of soft tissue.

Case 1 suggests that patients with deficient soft tissue and scarring of the vocal cord can benefit from external medialization of the vocal cord. It seems that the tunnel technique can provide relief of aspiration in patients with paralysis due to central lesions, who often have concomitant superior laryngeal nerve and pharyngeal dysfunction, as well as in patients who have a lateralized vocal cord paralysis. This can be related to the slight reduction in the subglottic lumen produced by the implant (Fig 4B), which was found also in the cadaver dissections. Three of the patients in whom the tunnel technique was performed had clinical improvement of their aspiration. Both techniques of external medialization gave good functional results, and four of the five patients obtained a normal or nearly normal postoperative voice.

The granuloma formation in the anterior commissure in one of the dogs probably is related to an excessive medialization of the vocal cord. We did not observe the development of diplophonia, which might have occurred with the tunnel technique, in either the dogs or the five patients. There was no damage of the subglottic mucosa or cricothyroid joint luxation.

This study clearly shows how these techniques work. The Silastic produced a minimal fibrotic reaction, and its easy removal after a 2-month period is additional evidence that these external procedures are reversible. The degree of lateral compression may be adjusted better by using Koufman's technique than by the tunnel method, and the former is ideal for medialization of the vocal cord after a peripheral nerve lesion. The use of perichondrium of the TC to seal the defect created on it will help stabilize the implant and prevent early extrusions.

Both techniques may be used in conjunction with the procedure of vocal ligament tightening popularized by Isshiki et al,[14] LeJeune et al,[17] and Tuck-

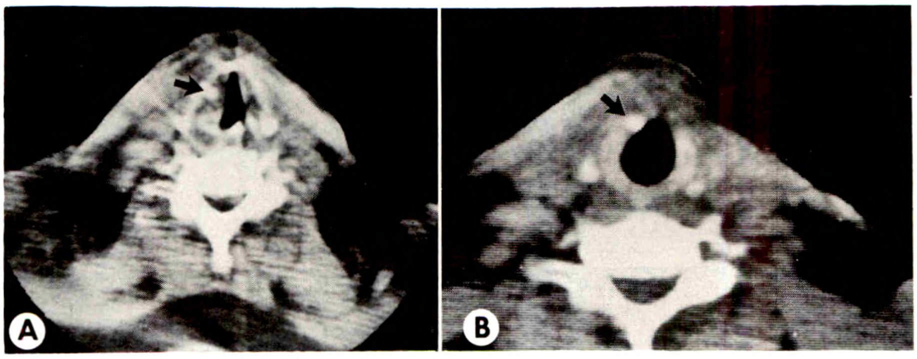

Fig 4. (Case 3) Computed tomographic scans. A) Scan showing Silastic implant after tunnel technique was performed on left side of larynx in order to medialize vocal cord (arrow). Following procedure, patient obtained nearly normal voice. B) Scan at level of subglottic region, showing slight reduction of lumen secondary to Silastic implant (arrow). There is no damage to mucosa or emphysema around implant.

er[18] for management of flaccid larynges or for patients who desire a modification of basic vocal pitch. Laryngeal reinnervation techniques such as the ansa hypoglossi–recurrent laryngeal nerve anastomosis[5] can be used as well, thanks to the reversibility of the procedure, and may offer the patient a more physiologic method of restoring vocal cord movement after unilateral paralysis. Once vocal cord mobility is regained, the laryngeal implant will be removed in order to avoid secondary problems.

It seems that external medialization of the vocal cord overcomes some of the inconveniences of Teflon injection and offers a new area for research in phonosurgery.

CONCLUSIONS

1. A new technique for vocal cord medialization is presented, using medical grade Silastic in a pocket created in the inner perichondrium of the TC (tunnel technique).
2. Early experiences have been promising in patients with paralysis due to central lesions, as well as in patients with lateralized vocal cord paralysis. Aspiration can be improved, and this constitutes an advantage over Koufman's procedure.
3. A modification of Koufman's laryngoplasty technique is presented, using the external perichondrium of the TC to keep the Silastic implant in place over the previously formed window. Experience has shown that several pieces of Silastic were needed in order to get voice improvement.
4. These techniques of external mobilization have a low morbidity. They are reversible and may be used in combination with other techniques of rehabilitation of the movement of the vocal cords, such as the ansa hypoglossi–recurrent laryngeal nerve anastomosis.
5. External mobilization of the vocal cord constitutes a good alternative to the Teflon injection method.

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PROTOCOL FOR MANAGEMENT OF THE INTERPOSITION CARTILAGE GRAFT LARYNGOTRACHEOPLASTY

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This report presents the results of laryngotracheoplasty surgery using both the Evans and Cotton techniques on 27 children with congenital or acquired subglottic stenosis. Failure to obtain early decannulation after surgery has resulted in the formulation of a new protocol for the operative and postoperative management of infants undergoing cartilage graft tracheoplasty. Excision and closure of the tracheostoma at surgery, with postoperative nasoendotracheal intubation providing the necessary support for the graft, now has reduced this period to approximately 2 weeks. A series of six infants for whom this protocol was followed is presented.

KEY WORDS — cartilage graft laryngotracheoplasty, endotracheal intubation, tracheostoma closure.

INTRODUCTION

Upper airway obstruction is a common problem in pediatric otolaryngology. Of the children affected, those with laryngeal obstruction tend to present a more acute problem than those with nasal or pharyngeal obstruction. When there is an underlying laryngeal stenosis, tracheotomy is usually required and may have to be maintained for a prolonged period, according to Fearon and Ellis[1] and Holinger et al.[2] A chronic tracheotomy represents a major management problem both in terms of prolonged hospitalization and the risks attendant on tracheotomy in infancy. In recent years, efforts have been directed toward surgical correction of subglottic stenosis in order to reduce the period of time for which tracheotomy is required. In 1974, several authors published pioneering work on this. Andersen et al[3] described a vertical midline split through the stenotic area with subsequent distraction maintained with an endotracheal stent. Fearon and Cotton[4] similarly described a vertical midline split through the stenotic area, but maintained distraction with a cartilage interposition graft. Evans and Todd[5] described a castellated vertical incision through the stenotic area, which was sutured to maintain distraction.

At the Red Cross War Memorial Children's Hospital in Cape Town, the usual mode of presentation of congenital subglottic stenosis is that critical airway obstruction is precipitated by acute laryngotracheobronchitis (croup). This is a common condition here, 500 to 600 such children being seen each year, of whom half will require admission and one in five, endotracheal intubation. Tracheotomy is performed either when congenital subglottic stenosis is suspected strongly at intubation or when it subsequently manifests as failure of successful extubation. This occurs in 3% to 5% of these patients, of whom one in three will require corrective surgery before successful decannulation. Acquired subglottic stenosis usually presents when patients have been intubated in uncontrolled circumstances for some other reason — often head injury. Airway obstruction becomes apparent soon after extubation when edema develops in the underlying damaged mucosa of the larynx. Granulation tissue thereafter appears in the ulcerated areas, and as this heals over a period of time, scarring and contracture permanently narrow the airway.

EVANS AND COTTON PROCEDURES

At this hospital, surgical correction of subglottic laryngeal stenosis in children was undertaken first in 1978. Between 1978 and the end of 1984, 27 children underwent corrective surgery. The method described by Evans and Todd[5] was used until the beginning of 1984, after which time a change was made to that described by Cotton.[6]

Thirteen children had congenital subglottic stenosis. In correction of ten of these, the Evans surgical technique was used: seven were extubated at times ranging from 6 weeks to 3 years after surgery. (One child required a second procedure.) One child with Hurler's syndrome was lost to follow-up after transfer to another hospital. A second child developed necrosis of the anterior aspect of the upper tracheal cartilages, and eventually, after 5 years, this was corrected successfully using a cartilage graft. A third child, who after removal of the stent developed a thin upper tracheal web, still wears a corked tracheotomy tube for occasional aspiration of accumulated secretions. Of the three children operated on by the Cotton technique, all were decannulated between 4 and 6 months postoperatively.

Fourteen children had acquired subglottic stenosis. In correction of 11 of these, the Evans surgical technique was used: nine were successfully decannulated at periods ranging from 6 weeks to 3 years

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RESULTS OF NEW MANAGEMENT PROTOCOL

Patient at Admission					
Sex	*Age (mo)*	*Indication for Tracheotomy*	*Underlying Disorder*	*Duration of Tracheotomy*	*Surgical Procedure*
M	14	Laryngotracheobroncholitis	Congenital subglottic stenosis	6 mo	Laryngotracheoplasty with anterior cartilage graft, 4-mm endotracheal tube
M	24	Laryngotracheobroncholitis requiring tracheotomy on 3 occasions	Congenital subglottic stenosis	2 mo	Laryngotracheoplasty with anterior cartilage graft, 4-mm endotracheal tube
F	5	Laryngotracheobroncholitis	Congenital subglottic stenosis	18 mo; failed laryngotracheoplasty 6 mo after primary admission	Laryngotracheoplasty with anterior cartilage graft, 4-mm endotracheal tube
M	3	Postintubation airway obstruction. (Inguinal hernia repair. Postoperative pneumonia requiring intermittent positive pressure ventilation.)	Acquired subglottic stenosis	7 mo	Laryngotracheoplasty with anterior cartilage graft, 4-mm endotracheal tube
M	9	Postintubation stridor. (Inguinal hernia repair.)	Congenital subglottic stenosis	—	Primary laryngotracheoplasty with anterior cartilage graft, 4-mm endotracheal tube

after surgery. (One child required a second procedure.) One child was lost to follow-up after transfer to another hospital. Another child developed a posterior commissure stricture, which still requires correction before attempting decannulation. Three children were operated on using the Cotton technique. One was decannulated after 3 months. A second had restenosis after removal of the stent and required a second procedure before successful decannulation. The third, who has a tendency to keloid scarring, has redeveloped a dense fibrous stricture.

These results were not encouraging, in terms of reducing the period of time for which a tracheotomy was required. The major problem experienced was persistent inflammatory induration of the soft tissues within the lumen of the larynx and upper trachea, often with associated granuloma formation. This reaction only gradually resolved to the point at which the lumen was of sufficient diameter to allow decannulation.

With the Evans technique, it was found that the Silastic Swiss roll excited profuse granulation tissue formation, particularly about its upper end. When a change was made to a simple Silastic tube stent, the reaction was less but still present. With a change to the Cotton technique and a Teflon stent, it was hoped that this problem would be resolved, but the granulation tissue reaction about its upper end proved to be even worse. Why these problems should have occurred at this institution, not having been reported as occurring from other centers, was a cause for major concern and reflection.

It was concluded that the underlying cause was probably related to a localized, chronic, low-grade infection in the tissues of the larynx and upper trachea despite the use of perioperative and postoperative antibiotics. This appeared to be exacerbated by the presence of the foreign body that the stent represented. Almost certainly, the source of this infection was the colonized tracheotomy site. Infection from the stomal area followed the lines of exposed raw tissue left by the procedure. With the Evans technique, this was visible in the form of localized granuloma formation in the anterior tracheal wall after removal of the stent, and with the Cotton technique by the presence of granulation tissue around the margins of the cartilage graft.

NEW OPERATIVE AND POSTOPERATIVE MANAGEMENT PROTOCOL

In an attempt to overcome the problems mentioned above, the surgical technique and postoperative management have been revised since the beginning of 1985. At surgery, the infant is anesthetized via the existing tracheotomy tube. During preparation and draping for surgery, this is changed for a sterile anesthetic tube and connections. A portion of sixth costal cartilage is harvested and stored in normal saline, and that incision is closed and dressed. The larynx and trachea are exposed through an incision incorporating the tracheostoma. A midline vertical incision through the tracheal cartilages above the stoma is extended superiorly through the stenosis and overlying cricoid cartilage.

The anesthetist then passes a soft nasoendotracheal tube of a diameter that fits snugly, but not tightly, in the lower trachea, and the anesthetic tube in the tracheostoma is removed. The stomal tissue and any peristomal granulations are excised. The cartilage previously harvested is shaped and sutured in place as described by Cotton[6] to distend the cricoid and upper tracheal cartilages over the endotracheal tube, which then acts as the stent. The wound is washed well, sprayed with an antiseptic powder, and closed in layers with an incorporated corrugated rubber drain. A nasogastric feeding tube is passed and the anesthetic discontinued.

Postoperatively, the child is nursed in the pediatric respiratory unit. Intravenous antibiotics

RESULTS OF NEW MANAGEMENT PROTOCOL (continued)

Patient at Admission		*Duration to First Change of Tube (d)*	*Duration to Second Change of Tube (d)*	*Duration to Extubation (d)*	*Complications*	*Follow-up*
Sex	*Age (mo)*					
M	14	5	—	4	—	1 yr. No stridor, good voice despite one episode of respiratory tract infection and one episode of bleach ingestion. Discharged.
M	24	8	—	4	—	1 yr. No stridor, good voice despite two episodes of respiratory tract infection. Discharged.
F	5	5	5	2	—	1 yr. No stridor, good voice despite one episode of respiratory tract infection. Discharged.
M	3	6	3	4	Pneumonia. Intubated for 7 days for aspiration of secretions.	9 mo. No stridor, good voice despite three episodes of respiratory tract infection. Discharged.
M	9	—	—	4	Partial prolapse of graft 5 days after extubation. Intubated for further 13 days.	9 mo. No stridor, good voice despite contracting pulmonary TB, for which he remains on treatment.

(cephalosporin) started preoperatively are continued until after removal of the drain on the second postoperative day. The antibiotic thereafter is given via the nasogastric tube.

One week postoperatively, the nasoendotracheal tube is changed under anesthetic for a tube one whole size smaller (usually from 4 mm to 3 mm internal diameter). This step is necessary because the larger tube excites considerable edema of the tissues about the glottis. Three days later, extubation is attempted under general anesthesia. If it is successful, the child is returned to the respiratory unit, where any stridor that may develop is managed with nebulized adrenaline inhalations. Should there be no response to these, direct laryngoscopy under general anesthesia is performed with reintubation. Extubation is attempted again 3 days later.

RESULTS

This protocol has been followed with five infants (Table). Two were successfully extubated on the first attempt. Two required a second period of intubation. One of these, 3 days after extubation, developed bronchopneumonia with copious secretions and required a period of reintubation for aspiration of the secretions. With the last child, primary extubation was attempted on the fourth postoperative day (when it was noted that the perichondrium of the cartilage graft had not begun vascularization). Persistent stridor developed 5 days later, and laryngoscopy revealed that the cartilage graft had prolapsed partially into the subglottic lumen. Reintubation was required for a further 13 days before successful extubation. Laryngoscopy performed at extubation revealed that the perichondrium of the cartilage graft had become vascularized. In all children it was noted that the tracheostoma had healed by the time of extubation. There was no significant formation of granulation tissue around the cartilage graft. From the last case it has been concluded that the cartilage graft probably requires the support offered by the endotracheal tube for about 10 days before its perichondrium will have become vascularized from the adjacent mucosa and its cartilage firmly adheres to the adjacent trachea.

DISCUSSION

Failure of uniformly successful, early postoperative decannulation after laryngotracheoplasty can be attributed to inflammation and induration in the submucosal tissues of the larynx and upper trachea. The stent, necessary for support of the graft until it has become firmly adherent to the laryngeal and tracheal cartilages, acts as a foreign body and exacerbates the inflammatory reaction. The tracheostoma invariably is colonized by bacteria, and in some cases spread of organisms into the inflamed tissues occurs before healing can take place and predisposes the site to a state of low-grade, chronic infection. This exacerbates the induration, and granulation tissue appears in ulcerated areas. It is a basic surgical principle that infection around a foreign body is unlikely to resolve until the foreign body is removed. This would explain the exuberant growth of granulation tissue seen at times around the stent after laryngotracheoplasty.

Therefore, it would appear reasonable in such surgery to aim at closure of the tracheotomy with excision of its colonized stoma at surgery in order to remove this site of potential complications. Although it can be expected that the expanded subglottic area would provide an adequate postoperative air passage, the possibility exists that this may be rendered inadequate should edema develop. Further, the negative pressure that develops within the upper trachea during inspiration could predispose to inward prolapse of the graft before it has become firmly adherent. A period of postoperative endotracheal intubation would serve to prevent these potential complications. The tube would still be acting as a foreign body, but because it is only in situ for a short period of time, any infection that develops around it can be controlled with systemic antibiotics.

This small series of patients has been managed by a protocol that has demonstrated its effectiveness in reducing the period of postoperative intubation to between 10 and 20 days. This is an advance in laryngotracheoplasty surgery, and it is hoped that its presentation will be of interest to others working in this field.

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NINCDS NOTES*

RESEARCH GRANTS AVAILABLE

Grant applications to study dysphagia associated with neurologic disorders and to study progressive hearing impairment are currently being sought by the Division of Communicative and Neurosensory Disorders of the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS).

For the dysphagia research initiative, both basic and clinical investigators of the oral, pharyngeal, and laryngeal aspects of swallowing disorders (in patients with neurologic diseases) are encouraged to submit grant proposals.

Hearing loss proposals may include studies of 1) the pathophysiological bases of progressive hearing impairment, including the interaction of time, severity, and noise; 2) changes in auditory system neurotransmitters; and 3) animal model studies of disordered cochlear blood flow related to such factors as exposure to ototoxic agents and to noise.

For further information on dysphagia applications, contact Dr Judith Cooper, Division of Communicative and Neurosensory Disorders, NINCDS, Federal Building, Rm 1C-06, 7550 Wisconsin Ave, Bethesda, MD 20892; (301) 496-5061. For further information of progressive hearing loss proposals, contact Dr Ralph Naunton in Rm 1C-11 at the above address; (301) 496-1804.

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COMPARISON OF THE MICROBIOLOGY OF GROUP A AND NON-GROUP A STREPTOCOCCAL TONSILLITIS

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We studied the microbial flora of tonsils removed from 20 children who suffered from recurrent group A β-hemolytic streptococcal (GABHS) tonsillitis and 20 who had tonsillar hypertrophy following recurrent non-GABHS tonsillitis. Similar polymicrobial aerobic and anaerobic flora were recovered from the cores of the tonsils in each group. β-Lactamase-producing bacteria (BLPB) were recovered more often in the group with GABHS. This difference was due mostly to the lower incidence of β-lactamase-producing strains of *Branhamella catarrhalis* and *Bacteroides* sp in hypertrophic tonsils following non-GABHS tonsillitis. β-Lactamase-producing *Staphylococcus aureus* was found with equal frequency in both groups. These findings demonstrate that although BLPB are recovered more often in recurrently inflamed tonsils following GABHS infection, BLPB also can be found in hypertrophic tonsils following non-GABHS tonsillitis.

KEY WORDS — β-lactamase–producing bacteria, microbiology, tonsillitis.

INTRODUCTION

Recurrent tonsillitis due to group A β-hemolytic streptococci (GABHS) refractory to penicillin therapy is a common problem in children. The failure of penicillin to eradicate the infection has been attributed in part to the emergence of β-lactamase–producing aerobic and anaerobic bacteria.[1] These β-lactamase–producing bacteria (BLPB) may protect not only themselves from penicillin, but also, through the release of the enzyme into their environment, penicillin-susceptible bacteria such as GABHS.

Several studies have demonstrated the polymicrobial aerobic and anaerobic flora and the presence of BLPB in the core of tonsils removed from children with recurrent GABHS tonsillitis.[1-4] However, none of these studies evaluated the microbiology of tonsils removed from children with recurrent non-GABHS tonsillitis. Although GABHS are not recovered from these patients, antimicrobial agents are often administered to them.

This report describes a comparative study of the microbiology of core tonsillar specimens from children who had their tonsils removed because of recurrent GABHS tonsillitis, and from a similar group of patients who had their tonsils removed because of tonsillar hypertrophy secondary to recurrent non-GABHS tonsillitis. Comparison between these groups may shed light on the role of organisms other than GABHS in the causation of non-GABHS tonsillitis.

PATIENTS AND METHODS

The tonsils studied prospectively were removed from 20 patients who suffered from recurrent GABHS tonsillitis, and from 20 who had tonsillar hypertrophy associated with recurrent non-GABHS tonsillitis. Recurrent GABHS tonsillitis was defined as a disease of at least 2 years' duration, with at least three episodes of inflammation of the tonsils within the last year, in a patient from whom GABHS were recovered. All patients received multiple courses of antibiotics (average, 4.6 courses per child in the last year, 3.2 of which were penicillin), and all were given penicillin at least once. None received any antibiotic therapy for at least 1 month prior to surgery.

Tonsillar hypertrophy associated with non-GABHS recurrent tonsillitis was defined as a disease of at least 2 years' duration, in which the tonsils were hypertrophic and created an anatomic barrier impeding swallowing and breathing. Patients had several episodes of acute tonsillar inflammation associated with upper respiratory tract infection in which GABHS were never isolated from the pharyngotonsillar cultures. Antibiotic therapy including penicillin was administered in several of these instances in all of these children (average, 2.1 courses of antimicrobial therapy in the last year, 1.2 of which were penicillin). However, none received any antimicrobial therapy for at least 1 month prior to surgery.

Children's ages ranged from 4 years 3 months to 12 years 6 months (mean age, 9 years 8 months); 22 were boys and 18 were girls. The age and sex distribution was similar in the two groups. None of the patients had an active tonsillar infection at the time of tonsillectomy.

Immediately after excision, one of the tonsils was placed in a sterile Petri dish and held by forceps. One side of the tonsil was cauterized with a heated scalpel, and an incision was made through that

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MICROORGANISMS ISOLATED IN EXCISED TONSILS

	No. Isolates (No. β-Lactamase-Producing Isolates)	
Organisms	*20 Patients With Recurrent Tonsillitis*	*20 Patients With Tonsillar Hypertrophy*
Aerobic bacteria		
α-Hemolytic streptococci	15	16
γ-Hemolytic streptococci	13	10
Group A β-hemolytic streptococci	7	2
Group B β-hemolytic streptococci	2	3
Group C β-hemolytic streptococci	3	1
Group F β-hemolytic streptococci		1
Staphylococcus aureus	9 (9)	8 (8)
Staphylococcus epidermidis	2	3
Branhamella catarrhalis	10 (7)	9 (2)
Lactobacillus sp	3	5
Diphtheroid sp	3	3
Hemophilus influenzae type b	4 (1)	2
Hemophilus parainfluenzae	2 (1)	3
Eikenella corrodens	1	2
Escherichia coli	1	
Total aerobic isolates	75 (18)	68 (10)
Anaerobic bacteria		
Peptostreptococcus sp	18	20
Veillonella parvula	7	5
Bifidobacterium adolescentis	3	4
Eubacterium sp	3	2
Lactobacillus sp	4	6
Propionibacterium acnes	2	4
Actinomyces sp	5	3
Fusobacterium sp	7	9
Fusobacterium nucleatum	12	11
Bacteroides sp	10	6
Bacteroides melaninogenicus	6 (3)	7 (1)
Bacteroides asaccharolyticus	4 (2)	5 (1)
Bacteroides intermedius	11 (3)	11 (2)
Bacteroides oralis	6 (3)	5 (1)
Bacteroides oris-buccae	3 (1)	2
Bacteroides fragilis	2 (2)	2 (2)
Bacteroides distasonis	4	
Bacteroides uniformis	1	3
Bacteroides corrodens	3	2
Bacteroides ochraceus	2	1
Total anaerobic isolates	113 (14)	108 (7)
Total isolates	188 (32)	176 (17)

area, cutting the tonsil in half. The core of the tonsil was swabbed thoroughly with a sterile cotton-tipped applicator until the applicator was soaked with tissue. The applicator was introduced into an anaerobic transport medium (Port-A-Cul Swab system, BBL Microbiology Systems, Cockeysville, Md). The time between removal of the tonsils and inoculation of the specimen was never in excess of 1 hour. Specimens were inoculated onto 5% sheep's blood, chocolate, and MacConkey agar plates for the isolation of aerobic and facultative organisms. The plates were incubated at 37°C aerobically (MacConkey agar) or under 5% carbon dioxide and examined at 24 and 48 hours. For anaerobes, the material was plated onto prereduced medias: a vitamin K_1-enriched *Brucella* blood agar plate, an anaerobic blood agar plate containing kanamycin and vancomycin, and an anaerobic blood agar plate containing phenylethyl alcohol and an enriched thioglycolate broth (containing hemin and vitamin K_1).[5] The anaerobic plates and thioglycolate broth were incubated in GasPak jars (BBL Microbiology Systems) and examined at 48 and 96 hours. Anaerobes were identified by techniques previously described.[5] Aerobic bacteria were identified using conventional methods.[6] β-Lactamase activity was determined on all organisms by the chromogenic cephalosporin analog 87/312 method.[7] Statistical analysis was done using the χ^2 and Mann-Whitney tests.

RESULTS

One hundred eighty-eight organisms (75 aerobes or facultative anaerobes and 113 anaerobes) were isolated from the tonsils of the children with recurrent GABHS tonsillitis (see Table). Mixed flora were present in all the tonsils, yielding an average of 9.4 isolates per tonsil (3.75 aerobes or facultative anaerobes and 5.65 anaerobes).

One hundred seventy-six bacterial strains (68 aerobes or facultative anaerobes and 108 anaerobes) were recovered from the tonsils of the patients with tonsillar hypertrophy following non-GABHS tonsillitis. Mixed flora were present in all tonsils, yielding an average of 8.8 isolates per tonsil (3.4 aerobes or facultative anaerobes and 5.4 anaerobes).

Similar organisms were recovered in both groups, except for GABHS, which were isolated more often in the tonsils of children with recurrent GABHS tonsillitis. The aerobic organisms most frequently isolated in both groups were α- and γ-hemolytic streptococci, *Branhamella catarrhalis*, *Staphylococcus aureus*, β-hemolytic streptococci (groups A, B, and C), and *Hemophilus* sp. The predominant anaerobic organisms were *Bacteroides* sp (including *Bacteroides melaninogenicus* and *Bacteroides fragilis* groups), *Fusobacterium* sp, anaerobic gram-positive cocci, and *Veillonella parvula*.

β-Lactamase production was detectable in 32 isolates recovered from 17 of 20 tonsils (85%) from children with recurrent GABHS tonsillitis (1.6 BLPB per patient), and in 17 isolates recovered from eight of 20 tonsils (40%) from children with tonsillar hypertrophy following non-GABHS tonsillitis (0.85 BLPB per patient) ($p < .005$).

The BLPB were *S aureus*, *B catarrhalis*, *Hemophilus* sp, and *Bacteroides* sp. All strains of *S aureus* recovered from both groups of patients produced β-lactamase. However, there were differences in the recovery rate of β-lactamase–producing strains among the other bacterial species. While seven of ten (70%) *B catarrhalis* strains in recurrent GABHS tonsillitis produced the enzyme, only two of nine (22%) produced the enzyme in the other group ($p = .05$). Similarly, while 12 of 30 strains (40%) of *Bacteroides* sp that are normally part of the oral flora (*B melaninogenicus*, *Bacteroides oralis*, and *Bacteroides oris-buccae*) produced β-lactamase in the group with recurrent GABHS tonsillitis, only five of 30 (17%) produced the enzyme in the group with non-GABHS tonsillitis ($p < .05$).

DISCUSSION

This study confirms our previous observations of the polymicrobial aerobic and anaerobic flora recovered from the cores of inflamed tonsils following recurrent GABHS infections.[1-8] We chose to culture the core of the tonsils rather than the surface because of the higher recovery of GABHS as well as anaerobic bacteria from the core.[8] Core cultures also may better represent the true bacterial pathogens, rather than bacteria that colonize the surface.

The recovery of similar polymicrobial aerobic and anaerobic flora from the cores of hypertrophic tonsils after non-GABHS tonsillitis is a perplexing finding. A possible explanation is that these organisms, which are known colonizers of the surface of normal tonsils,[9,10] are also colonizers of the core of tonsils. This hypothesis can be examined by obtaining cultures from the cores of normal tonsils. However, since many of these organisms are potential pathogens,[9] they may have a role in the inflammatory process in non-GABHS tonsillitis. Whether the presence of these bacteria in the core of hypertrophic tonsils contributes to the pathologic process in these tonsils is yet to be determined.

Staphylococcus aureus, GABHS, *Streptococcus pneumoniae*, and viruses traditionally are associated with tonsillar and peritonsillar infections. However, anaerobes also have been isolated from the tonsils of children with chronic recurrent GABHS tonsillitis[1-8] and peritonsillar abscesses.[11]

The possible role of anaerobes in the acute inflammatory process in the tonsils is supported by several clinical observations: 1) the recovery of anaerobes as predominant pathogens in abscesses of tonsils or the retropharyngeal area, in many cases without any aerobic bacteria[11,12]; 2) their recovery as pathogens in well-established anaerobic infections of the tonsils (Vincent's angina)[13]; 3) the increased recovery rate of encapsulated *B melaninogenicus* in acutely inflamed tonsils[9]; and 4) the response to antibiotics in patients with non-GABHS tonsillitis.[14-18]

Several recent studies in which metronidazole was administered to patients with infectious mononucleosis supports the role of anaerobes in tonsillitis.[14,15] Metronidazole alleviated the clinical symptoms of tonsillar hypertrophy and shortened the duration of fever. Metronidazole has no antimicrobial activity against aerobic bacteria and is only effective against anaerobes.[19] A possible mechanism of its action could be suppression of the oral anaerobic flora that might have contributed to the inflammatory process induced by the Epstein-Barr virus.[14,15]

McDonald et al[16] demonstrated a reduction in the severity of symptoms of adults with non-GABHS tonsillitis following the administration of erythromycin. Merenstein and Rogers[17] demonstrated definite improvement in the symptoms of patients with acute non-GABHS tonsillitis following penicillin therapy as compared to placebo. Putto[18] showed an earlier reduction in fever following penicillin therapy in children with non-GABHS tonsillitis than in patients with viral tonsillitis. These findings suggest that bacteria other than GABHS, including anaerobes, may be involved in acute tonsillitis. However, since no proof of that hypothesis is available, these observations have no practical implications at present and await further studies.

We were able to detect BLPB in over three fourths of our patients, a finding that confirms previous data reported in children with recurrent GABHS tonsillitis.[1-4] We also were able to detect BLPB in tonsils recovered from 40% of children with tonsillar hypertrophy following non-GABHS tonsillitis. Although this is a lower incidence than in recurrent tonsillitis, this finding is not surprising, since all of these children had received penicillin therapy within the year prior to surgery.

The presence of BLPB in the cores of tonsils removed from children with either recurrent GABHS or non-GABHS tonsillitis may be attributed to previous penicillin therapy.[10,20] Since the patients with recurrent GABHS tonsillitis were treated twice as often with antimicrobial agents, it is not surprising that BLPB were found in more than twice as many tonsillar cores (85% versus 40%).

Previous studies have demonstrated the rapid emergence of BLPB following penicillin therapy.[10,20] Brook and Gober[20] isolated BLPB in three of 21 children (14%) prior to penicillin therapy, and in ten of 21 (48%) following one course of penicillin. The organisms were members of the *B melaninogenicus* group, *S aureus*, *B catarrhalis*, and *Hemophilus influenzae*. These organisms also were isolated from household contacts of children repeatedly treated with penicillin, suggesting their possible transfer within a family.[20] A similar shift in flora was noted when 98 patients with acute GABHS tonsillitis were treated with penicillin.[21] Fifty-eight BLPB were isolated prior to therapy, and 92 were found following therapy.

The isolation of BLPB from inflamed tonsils following GABHS and non-GABHS tonsillitis raises the question of whether the treatment of recurrent tonsillitis due to either GABHS or other flora with penicillin is adequate in all instances, and whether therapy should be directed also at the eradication of these organisms.

There are several clinical trials in children that support the administration of antimicrobial agents effective against both aerobic and anaerobic BLPB in cases of recurrent tonsillitis.[10,22-24] In the most recent of these studies, clindamycin therapy was found to be superior to use of erythromycin or penicillin.[10] Other agents that may be effective in the therapy of this condition are the combination of the β-lactamase inhibitor clavulanic acid and amoxicillin and the combination of macrolides and metronidazole. Further studies are needed, however, to evaluate the efficacy of such therapies in acute inflammation in non-GABHS tonsillitis.

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Ann Otol Rhinol Laryngol 97 1988

CLINICAL INVESTIGATIONS OF ADDUCTOR SPASTIC DYSPHONIA

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Spastic (spasmodic) dysphonia (SD) may coexist with or reflect certain neurologic or psychogenic illnesses. The present study of four patients with adductor SD (ASD) revealed several consistent clinical findings and characteristics that could be differentiated, while other findings were not distinguishable. Oscillographic and spectral analyses suggested voice tremor as a component of the dysphonia in all ASD patients studied. Clinical neurologic and otolaryngologic findings were nonconfirmatory regarding a disease process or state.

KEY WORDS — adductor spastic dysphonia.

Spastic (spasmodic) dysphonia (SD) continues to prove enigmatic for speech-language pathologists, otolaryngologists, and neurologists. The cardinal signs of the adductor form of the disorder include effortful vocal straining, vocal harshness, and voice arrest due to laryngospasm in the midst of noneffortful phonatory periods. Adductor SD (ASD) may be neurologic in origin and manifest in isolation or as a component of the hyperkinetic dysarthria accompanying Meige's disease, Tourette's syndrome, torsion dystonia, spasmodic torticollis, and severe essential voice tremor.[1-10] In certain patients with ASD there is evidence for a brain stem locus,[11-13] although a cause for the disorder could not be identified in 14 of 29 patients studied by Schaefer.[11] It may also represent a conversion reaction or musculoskeletal tension voice disorder and therefore may be psychogenic in origin.[1,3,14]

Some patients with ASD defy etiologic classification, although they may have subtle neuropathologic and psychopathologic signs.[1,5,15,16] Their SD is generally resistive to speech and traditional pharmacologic therapy, yet some may respond to recurrent laryngeal nerve resection or botulinum toxin injections.[1,17-20] Careful clinical follow-up may yield a differential diagnosis, as in the patient described by Aronson[1] whose idiopathic SD worsened and who on 3-year reexamination had developed dystonia and anterocollis. Similarly, Ludlow et al[13] described abnormal prephonatory muscle activation patterns from laryngeal electromyographs (EMGs) for five patients diagnosed as having idiopathic SD suggesting a central disorder. Electromyography, laryngeal vibration, movement, and perceptual and acoustic measures for one patient diagnosed as having idiopathic SD revealed various degrees of tremor both before and after recurrent laryngeal nerve block and resection.[15] Tremor also was identified from acoustic, perceptual, and visual measures for a heterogeneous population of SD patients.[21]

It has been suggested that the majority of patients with SD have an underlying movement disorder, most likely a dystonia.[22-24] In one report, six of 28 patients were thought to have voice signs consistent with a functional voice disorder or vocal abuse, while two could not be classified.[22] Blitzer et al[23] classified all 14 SD patients they studied by EMG as having a focal laryngeal dystonia, even though seven (50%) had essentially normal results. Following elective recurrent laryngeal nerve crush, two patients had, not unexpectedly, signs of lower motor neuron involvement.

Because irreversible recurrent laryngeal nerve resection continues to be the principal therapy for ASD, differentiation among the types of the disorder appears critical for patient selection and prescription of treatment. In this investigation we sought to examine clinical and acoustic characteristics of four patients diagnosed as having ASD. We felt that information gleaned from this study would assist in delineating the characteristics of this disorder and therefore add to the refinement of current diagnostic and assessment procedures.

METHODS AND PATIENTS

Four women ranging in age from 25 to 42 years and diagnosed by the investigators as having ASD served as subjects. The mean age of onset for the voice disorder was 26.5 years, while age at evaluation averaged 32.0 years. The duration of the disorder averaged 5.5 years prior to evaluation for this study. For certain analyses, four age-sex matched speakers with no history of speech or language, otolaryngologic, neurologic, psychiatric, or hearing

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disorders served as controls. Additionally, representative patients with ASD of neurologic and psychogenic cause were studied for comparison.

A comprehensive motor speech examination was completed by the senior author for each patient, and notation was made of all aberrant speech signs using accepted descriptors.[25] Each patient's speech, including a sustained /a/ rendered at falsetto, modal, and glottal fry registers, was recorded on a high quality audio cassette system (Newcomb model EDC-100). The audio signal of each patient's sustained /a/ was rectified, low pass filtered (30 Hz, 2 pole Butterworth), and displayed on a Grass (model 8-10) eight-channel oscillograph at 30 mm/s. As in earlier reports, these oscillographic records were analyzed for regular amplitude variations that were interpreted to reflect patterns of voice tremor and/or arrest.[5,26-28] That is, each tape-recorded sample of the patient sustaining /a/ was played back while being fed simultaneously into the oscillograph that traced the changes in intensity. The amplitude variations then were counted jointly and individually by the investigators. There was virtually 100% agreement that oscillographic variations in amplitude were accompanied by periodic audible changes in volume. Each sample of /a/ was at least 8 seconds in duration, allowing averaging of three 1-second segments per patient. Additionally, the rectified and low pass filtered (40 Hz, 2 pole Butterworth) acoustic signal from the sustained /a/ was subjected to spectral analyses using a Hewlett-Packard (3582A) spectrum analyzer providing an accuracy of 0.75 Hz. All patients underwent complete clinical otolaryngologic and neurologic examination. Otolaryngologic examination used both mirror and rigid endoscopic techniques for assessing laryngeal function. It was the consensus among the investigators that there were no signs of psychologic/psychiatric disorder.

Patient 1. A 25-year-old woman revealed a nonresolving voice disorder of insidious onset beginning at age 18. She was seen elsewhere at age 18 and was diagnosed as having idiopathic SD. Since onset, periodic symptomatic voice therapy proved equivocal in alleviating the symptoms. The voice signs had not worsened, although the patient noted that when she was anxious or under stress it was more difficult for her to produce voice. Although she denied an immediate family history of a movement disorder, she did note that her uncle was "a little shaky." There was no history of psychosocial discord or stress, and she described her family life as happy. She had no other complaints regarding speech and had not experienced dysphagia, dyspnea, or nasal reflux. She was not taking medication.

Patient 2. A 29-year-old woman had undergone cesarean section under general anesthesia 1 year prior to examination. Four days following discharge from hospital, she experienced a rather acute deterioration in voice. She had not been intubated for surgery. She denied dysphagia, dyspnea, or nasal reflux. There were no signs of endocrine dysfunction. She denied other changes in speech or language. Although the cesarean section was psychologically traumatic, she gave birth to a normal infant and "felt fine" postoperatively. Since giving birth, she had been taking birth control pills (Ortho-Novum) for approximately 1 year. There was no family history of a similar voice problem or movement disorder. However, she indicated that prior to her surgery she had "always had a peculiar voice" (to her, low pitched), while since surgery her voice deteriorated with fatigue and protracted use. She denied depression; there was no history of psychoemotional discord. She was the mother of two children and described her married life as happy. She had never received treatment for the voice symptoms. She was not taking medication.

Patient 3. A self-referred 32-year-old woman had been diagnosed by speech pathologists elsewhere as having ASD. She had served as a subject for an earlier study of the disorder.[15] Her voice disorder began insidiously 11 years prior to examination, with only occasional upward pitch breaks without voice arrest. Her symptoms had worsened gradually over the 11 years since onset, a not uncommon trend for ASD patients.[1,29] Her father and brother reportedly had an action tremor of the hands, the symptoms being worse in her brother, who also had voice tremor. Their symptoms had not been confirmed medically, however. The patient's voice symptoms worsened with fatigue, stress, and anxiety and with talking on the telephone or in front of a group. She reported improvement in voice with ingestion of alcohol and relaxation. She noted that her hands periodically shook, although there had been no deterioration in handwriting. She had received periodic concentrated symptomatic voice therapy from 1976 through 1981 without amelioration of the symptoms. She underwent a tonsillectomy in 1973 followed by administration of diazepam (Valium) for treatment of the voice symptoms. Neither treatment improved her voice. She was not taking medication during the study. She did not complain of other changes in speech, nor had she experienced dysphagia, dyspnea, or nasal reflux.

Patient 4. A 42-year-old woman complained of an insidious change in voice beginning approximately 3 years prior to examination. Since onset, the patient had not experienced remission nor been free of the voice symptoms; she did note that the symptoms were exacerbated by headache, anxiety, or fatigue. There was no familial history of a movement disorder. She had not experienced dysphagia, dyspnea, nasal reflux, or other changes in speech. She denied depression or psychoemotional discord. She had never received therapy for the voice symptoms. She was not taking medication.

SPEECH, NEUROLOGIC, AND OTOLARYNGOLOGIC FINDINGS FOR PATIENTS WITH ADDUCTOR SPASTIC DYSPHONIA

	Age (yr)		Duration of Voice Disorder	Speech Pathology Examination				
Patient	At Onset of Voice Disorder	At Examination	(yrs)	Perceptual	Oscillographic	Spectral	Neurologic Examination	Otolaryngologic Examination
1	18	25	7	va, hsh, strn, np	Irregular variations	4.6	Cogwheel rigidity left arm	Laryngeal synkinesis
2	28	29	1	va, hsh, strn, np, (?) tmr	Irregular variations; 6-Hz tremor on termination	5.4	(?) quick movements of facial muscles	Irregular movements
3	21	32	11	va, hsh, strn, np, artc, hd mnt	Protracted onset, (?) 6-Hz tremor	6.5	Normal	Laryngeal hyperadduction
4	39	42	3	va, hsh, strn, fmc, np, (?) ibm	Irregular variations	4.4	Normal	Normal
Mean	26.50	32.00	5.5			5.2		
Range	18-39	25-42	1-11			4.4-6.5		

va — voice arrest, hsh — harshness, strn — strain, np — noneffortful phonation, tmr — tremor, fmc — facial muscle contraction, ibm — intermittent breathy moments, artc — articulation errors, hd mnt — head movement, (?) — question of.

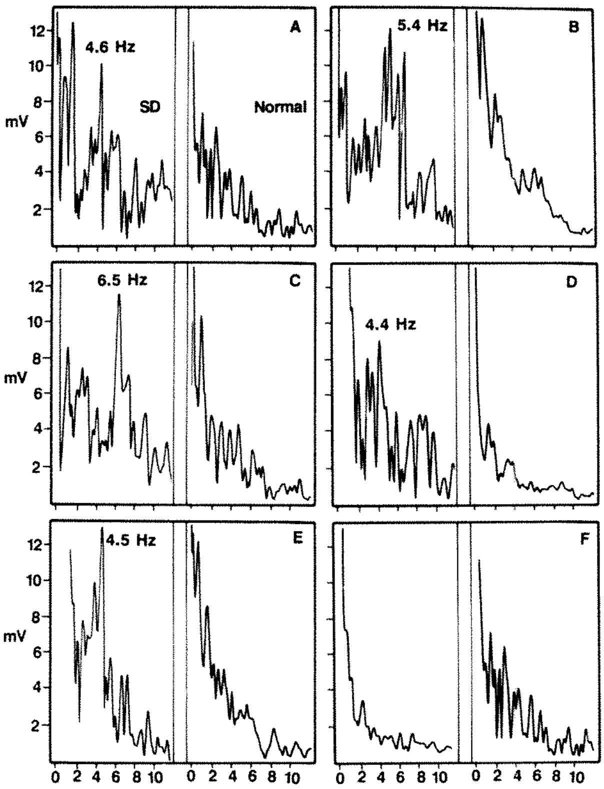
RESULTS

The Table summarizes the clinical findings and the results of the oscillographic and spectral analyses for each of the four patients. Spectral analyses of the sustained vowel signals revealed low frequency peaks that averaged 5.2 Hz (range, 4.4 to 6.5 Hz) for the ASD patients, with no discernible peaks for the matched controls. Generally, the acoustic envelope of the control subjects manifested similar spectral characteristics.

The conversational speech of patient 1 was marked by instances of partial and complete voice arrest occurring particularly on vowels followed by periods of noneffortful phonation. Moderate vocal harshness and straining were apparent throughout speech, with intermittent periods of noneffortful phonation. On prolonged phonation of the vowel /a/, these features were again present, although irregular changes in volume were also evident. Oscillographic analysis revealed irregular changes in intensity and instances of mild voice arrest consistent with vocal fold hyperadduction and laryngospasm. As shown in the Figure, A, spectral analysis of the prolonged /a/ revealed a peak at 4.6 Hz with prominent amplitude, while the control subjects demonstrated no prominent peaks. Neurologic examination suggested mild cogwheel rigidity of the left upper extremity. Laryngologic examination revealed quick synkinetic adductory movement of the true vocal cords, ventricular folds, and much of the supraglottis on prolonged vowel phonation. These movements occurred when harshness and voice arrests were perceived.

The conversational speech of patient 2 was marked by moderate vocal harshness, straining, and occasional mild adductor voice arrest interspersed with periods of noneffortful phonation. These signs were evident also on prolonged vowel phonation along with a question of vocal tremor, particularly at the termination of the sound. Oscillographic analysis revealed irregular changes in intensity with small amplitudes. However, at the termination of phonation, regular changes in intensity averaging 6 Hz were noted. Spectral analysis revealed multiple peaks centered at 5.4 Hz with prominent amplitude (see Figure, B) in comparison to no prominent peaks for controls. Neurologic examination suggested periodic quick low amplitude movements of the nasalis muscles bilaterally and the orbicularis oris when the patient was not speaking. Laryngologic examination revealed vocal fold approximation to be normal but with small irregular movements on the superior surface of the true vocal cords on prolonged vowel phonation. These movements were judged to occur when harshness and straining were perceived. A 1-week period of speech therapy 1 hr/d proved unsuccessful in improving the voice.

The conversational speech of patient 3 was marked by instances of both partial and complete adductor voice arrest frequently lasting approximately 1 second, occurring particularly on vowels and followed by islands of noneffortful phonation. Vocal harshness and straining were judged to be severe and were apparent throughout speech, with the features being particularly evident at the onset of a sustained vowel. Instances of sound (particularly vowel) repetition and distortion occurred with voice arrest. Occurring in synchrony with voice arrest were quick depressive movements of the mandible and flexion of the head. Prolongation of /a/ at all vocal registers revealed harshness, straining, irregular changes in volume, and islands of noneffortful phonation. Oscillographic analysis revealed irregular protracted voice onset and a question of regular changes in intensity occurring at 6 Hz. Spectral analysis revealed a sharp peak at 6.5 Hz of high amplitude (see Figure, C). Neurologic examination was normal. Laryngoscopy revealed periodic laryngospasm marked by compression of the aryepiglottic folds, hyperad-



Spectrum of low frequency energy in rectified and low-pass filtered acoustic signals recorded during sustained /a/ phonations. A-D) Left portions show spectra in female adductor spastic dysphonia (ASD) patients 1, 2, 3, and 4, respectively. Right panels show spectra for matched normal controls. E,F) Left portions show spectra for two patients with diagnoses of ASD of essential voice tremor and psychogenic ASD, respectively. Right portions show spectra from matched controls. Amplitude scale is relative to playback level for individual subjects; absolute calibration was not warranted.

duction of the arytenoid cartilages, and obscuration of the glottis by the ventricular folds. Perceptually, these movements were concurrent with voice arrest.

The conversational speech of patient 4 was marked by adductor voice arrest most apparent on voiced consonants and vowels, while moderate vocal harshness and straining were apparent throughout contextual speech. There was a question of occasional intermittent breathy dysphonic moments.[27] Contraction of the frontalis muscle bilaterally, with resultant elevation of the brows, occurred periodically in conjunction with adductor voice arrests. Vowel prolongation, particularly at onset, revealed irregular changes in volume. With continuation, periods of noneffortful phonation were evident. Oscillographic analysis revealed irregular changes in intensity with variable amplitude. Spectral analysis revealed a broad peak centered at 4.4 Hz with prominent amplitude (see Figure, D). Both neurologic and laryngologic examinations were normal. One week of speech therapy 1 hr/d and a trial of propranolol did not improve the voice signs. She declined further treatment.

For comparison, the spectral analyses of two patients with ASD of essential voice tremor and psychogenic ASD were included. Although they did not participate in the present study, both had undergone the same rigorous evaluations as the ASD patients. Both patients had received therapy for their voice disorders. The 55-year-old woman with ASD of essential voice tremor did not benefit from pharmacologic or behavioral treatment. Although older than the patients in the present study, she adequately represented patients with this disorder.[5] The Figure, E, shows a peak at 4.5 Hz with large amplitude for the patient with ASD of essential voice tremor. The 22-year-old woman with psychogenic ASD was relieved of her dysphonia completely with behavioral voice therapy and has remained free of signs. The Figure, F, shows the spectral analysis from that subject; it is comparable to that for the matched control, inasmuch as there is no prominent spectral peak.

DISCUSSION

Although the data from the present investigation are based on a small sample, SD, including the adductor form, is a rare disorder, making the findings of some importance. In the present study, the average age of onset for the dysphonia was notably less than previously reported.[2,3,29] With the exception of the one patient reported by Lang and Marsden,[10] they were also generally younger than patients who demonstrated a neurogenic substrate for the SD.[5,8] In the present study, all patients were women; however, this may have been coincidental.

Three of the four patients reported an insidious onset of the dysphonia and a nonresolving course. Although patient 2 identified acute deterioration in voice following cesarean section, she also indicated that her voice had always been unusual prior to surgery. All patients noted exacerbation of the symptoms and signs with psychoemotional stress; patient 4 noted deterioration particularly with headache. None of the patients had a confirmed family history of a movement disorder, although the action tremors described by patient 3 for her father and brother as well as "tremor" of the voice in the latter makes a hereditary component suspect in this case. Only one patient (patient 3) experienced amelioration in the symptoms with alcohol use, while none of the patients, including the two treated during the course of this study, experienced significant benefit from either speech or trial drug therapy. Only patient 3 reported that the voice symptoms had significantly worsened since onset. The majority of the aforementioned findings are not inconsistent with those for all forms of ASD.[1]

The perceptual findings for all four patients are consistent with those delineated for ASD. Acoustically, however, the picture is somewhat less clear. Oscillographically, irregular intensity changes were noted for all patients, although a 6-Hz tremor was suggested at the termination of the sustained vowel for patient 2 and there was a question of a comparable tremor frequency for patient 3. Neither, however, could be confirmed from visual analysis. In an earlier study, Hartman et al[15] questioned the presence of a 6-Hz tremor from oscillographic analysis in one patient with idiopathic ASD. Spectral analyses of the sustained /a/ voice signal, lip and jaw isometric forces, and EMG from select facial and extrinsic laryngeal muscles also revealed tremor. The voice tremor persisted on repeated acoustic and physiologic analyses, following recurrent laryngeal nerve anesthesia and subsequent elective resection. Notably, ten of 29 patients with ASD of unknown cause reported by Schaefer[11] had voice tremor. For the four patients in the present investigation, oscillographic amplitude changes were more irregular than those previously described for patients with essential voice tremor, patients with ASD of essential voice tremor, and the one patient identified (although not studied) as having idiopathic ASD.[5]

Spectral analyses consistently showed low frequency and high amplitude peaks on vowel prolongation for the ASD patients in comparison to the matched normal controls. Similar findings have been described for enhanced physiologic and essential tremor of the limbs, and for the lips and extrinsic laryngeal musculature in one patient with idiopathic ASD.[15,30-32] For the four patients studied here, the mean frequency of 5.2 Hz as well as the range (4.4 to 6.5 Hz) is well within the frequency range of both essential voice tremor and ASD of essential voice tremor.[5] However, for our patients, the tremor intensity changes may not have been as perceptible, because of their lower comparative amplitudes — a finding noted recently by Muller et al[16] as well for four of 22 patients with ASD. The /a/ phonation spectrum from the patient with psychogenic ASD was more like that of the normal controls, while the patient with ASD of essential voice tremor demonstrated spectral peaks that resembled those in ASD. It is conceivable that some patients with ASD have abnormal neuromotor processes with resultant tremor, a condition frequently accompanying other disorders of movement.[8,31-33,34] However, whether the voice signs in our patients were forme fruste and pathognomonic of a movement disorder needs to be investigated further. Tremor in other parts of the body presents comparable problems in interpretation of cause, differential diagnosis, prognosis, and treatment.[31-33,34] Despite these problems, however, the consistency of the spectral findings suggests that such analyses may prove useful in further delineating the signs of ASD.

Clinical neurologic and otolaryngologic examinations were useful in identifying subtle changes in the neuraxis and laryngeal mechanism, but did not provide confirmatory diagnoses. No patients were judged clinically to have signs of dystonia, although extrapyramidal features were identified. Perhaps the findings from the present study would have been enhanced by laryngeal EMG and auditory brain stem function testing.[11-13] Follow-up examinations of the four patients may provide opportunities to use them.

A consensus has yet to be achieved regarding the existence of forms of ASD. The combination of 1) timing of evaluation in relation to the disease state and 2) regular reexamination is tantamount to a differential diagnosis of the disorder. In the absence of confirming neuropathologic or psychopathologic signs, the etiologic determination of ASD is at best tentative. We agree with Aronson,[1(p182-183)] who states:

> "The category of idiopathic adductor-spastic dysphonia is not diagnostic but a means of placing the diagnosis in suspense until further data have been acquired to show a definite etiology. If the patient is suitably followed over a long period of time, a psychogenic or neurologic etiology often will reveal itself, permitting a change of classification."

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INTERNATIONAL WORKSHOP ON CRANIO-FACIAL TRAUMA

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ACQUIRED ULTRASTRUCTURAL ALTERATIONS OF RESPIRATORY CILIA AND CLINICAL DISEASE

A REVIEW

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Efficient cleansing of the upper and lower respiratory surfaces by the mucociliary apparatus is essential to health. Failure of the cleansing allows contaminants prolonged residence on the mucosal respiratory surfaces and thus penetration into the mucosa and possibly inauguration of disease. For some years, genetic ultrastructural ciliary alterations have been recognized, with symptoms dating from early life. It is only in recent years, however, that evidence has shown that ultrastructural ciliary alterations can be acquired later in life and that these alterations in turn lead to a deterioration of efficient ciliary cleansing. A discussion of the ultrastructure of the normal mammalian cilium will be given, as well as a listing of the genetic ciliary diseases and their characteristic morphologic alterations. A more complete review will be made in regard to acquired ciliary defects, their cause, the ultrastructural changes, and the relation to clinical disease.

KEY WORDS — acquired ciliary alterations, cilia, congenital ciliary alterations, ultrastructural ciliary alterations.

One of the principal functions of mammalian respiratory cilia is keeping respiratory surfaces clean. Failure to do this may be an important step in the inauguration of disease by permitting inhaled, noxious environmental substances or noxious products of infection deposited on the respiratory surface sufficient time to penetrate to the deeper cells. The principal concern in preparing this manuscript has been to investigate the effects these noxious substances might have on normal-functioning mucociliary cleansing and thus, as stated above, also on the inauguration or perpetuation of respiratory disease. It is the thesis of this paper that the inauguration of nasal disease and the symptoms of such disease, including the prolongation of the symptoms in some situations, likely are related to certain acquired ciliary defects.

Anatomically, the mammalian hairlike respiratory cilia project some 6 to 7 μm above the free surface of the mucous membrane into the lumen of the airway and are largely enveloped by thin periciliary fluid. When fully extended, the tips of the cilia penetrate flakes of mucus that float on the underlying periciliary fluid. Metachronous beating of the respiratory cilia approximately 1,000 or more times per minute propels the mucus with its contained foreign material to the upper end of the esophagus, where it is swallowed. The efficiency of this mucociliary cleansing can be compromised by several factors: 1) too great a depth of the periciliary fluid[1,2]; 2) too great a depth, too great a viscosity, or a significant decrease in the elastic recoil of the mucous layer[3,4]; 3) "tethering" of the mucus to the mucous glands[2] (Fig 1); and 4) ultramicroscopic deficiencies of the ciliary cytoarchitecture (described below). The last-named problem includes axonemal errors, as well as the recently described abnormal length[5] (Fig 2A) of the cilium and abnormalities of the basal apparatus and the ciliary neck-

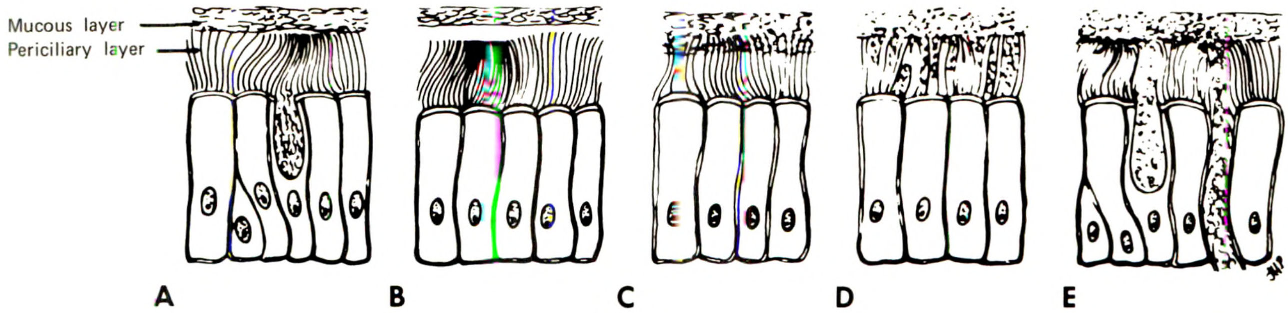

Fig 1. Diagram of cilia and possible relationships to mucous layer. A) In health, tips of cilia, when fully extended, penetrate undersurface of mucous flakes. B) Ciliary tips fail to penetrate mucous layer. C) Cilia penetrate too far into mucus. D) Mucous layer is so abundant that it has replaced periciliary fluid. E) Mucus is tethered to its source, mucous gland. (Adapted from Rossman et al.[16])

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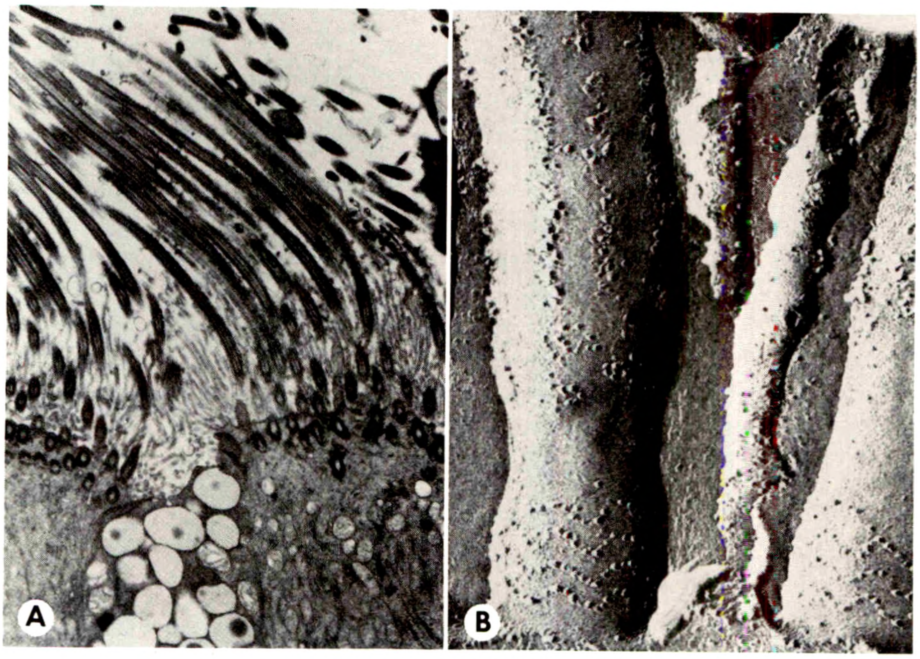

Fig 2. Electron microscopic views of cilia. A) Ciliated surface, showing abnormally long cilia. (Reprinted with permission.[5]) B) Ciliary necklace. (Reprinted with permission.[7])

lace. It is the deficiencies of the cytoarchitecture with which this paper is concerned. Some of these conditions are diagrammatically illustrated in the following Figures and descriptions. The important thing to realize is that the physiologic correlate of ciliary cytoarchitectural deficiencies is ciliary dyskinesia and mucostasis. In recent years, descriptions of the normal ultrastructure of respiratory cilia have been published,[6] though there is yet much to be discovered. Figure 3 depicts a diagrammatic cross section and longitudinal section of the midportion of a human respiratory cilium. In Fig 4, a diagrammatic three-dimensional view is shown, and in Fig 2B, the presence of a "ciliary necklace"[7] at the base of the cilium is noteworthy. This structure seems to be an integral part of ciliogenesis, along with the centriole–basal body assembly. Each "bead" of the necklace corresponds to a microtubular doublet. A fundamental question has been raised as to whether the basal bodies, which are the precursors of the cilia, contain RNA; this has not been satisfactorily answered.[8] Abnormalities of the basal bodies cause ciliary dyskinesia (Fig 5).

Microtubules are straight, hollow intracellular structures present in living cells; in the case of respiratory cilia, microtubules control the movement of the cilia. Motility of the respiratory cilia and that of the flagella and sperm tails depends on a special assembly of these tubules in nine peripheral doublets and a central pair of singlets, the so-called 9 plus 2 formation, in the axoneme of the cilium. Departure from the 9 plus 2 formation leads to altered ciliary movement and dyskinesia.

Sliding of tubule A of each peripheral doublet in relation to tubule B of the adjacent doublet is the mechanism responsible for the beating movement, with the dynein arms providing the ATPase for mechanochemical work.[9] The radial spokes also play a part in the movement by reattaching to the central pair of tubules as movement occurs. Loss of dynein arms or disturbance of the radial spokes leads to ciliary dyskinesia and mucostasis.

Cilia are found in the upper (nasal passages, paranasal sinuses, middle ears, and eustachian tubes) and lower respiratory tract (trachea to respiratory bronchioles). Spermatozoa are modified cilia; and retinal rods, vestibular hair cells, and olfactory cells are derived from similar prodromal structures. Congenital disruption of the ultrastructural ciliary apparatus can produce not only characteristic symptoms of the respiratory tract, but also of the modified ciliary sensory epithelia of the eye and ear. In congenital ciliary defects, symptoms are present from birth or develop in the first few weeks or months of life; the defects are widespread and have been found in the many locations in which cilia are located. The ultrastructural defects in congenital deficiencies are essentially the lack or attenuated state of development of the dynein arms or radial spokes. Several of these congenital syndromes, with some of their characteristic symptoms, are as follows.

1. Primary ciliary dyskinesia
2. Kartagener's syndrome[10] — chronic bronchitis, chronic sinusitis, rhinitis, and situs inversus (50%)
3. Polynesian bronchiectasis[11]
4. Chronic bronchitis
5. Retinitis pigmentosa — night blindness often associated with hearing loss (Usher's syndrome[12])
6. Laurence-Moon-Biedl syndrome — obesity, retinal degeneration, genital hypoplasia, mental retardation, and deafness

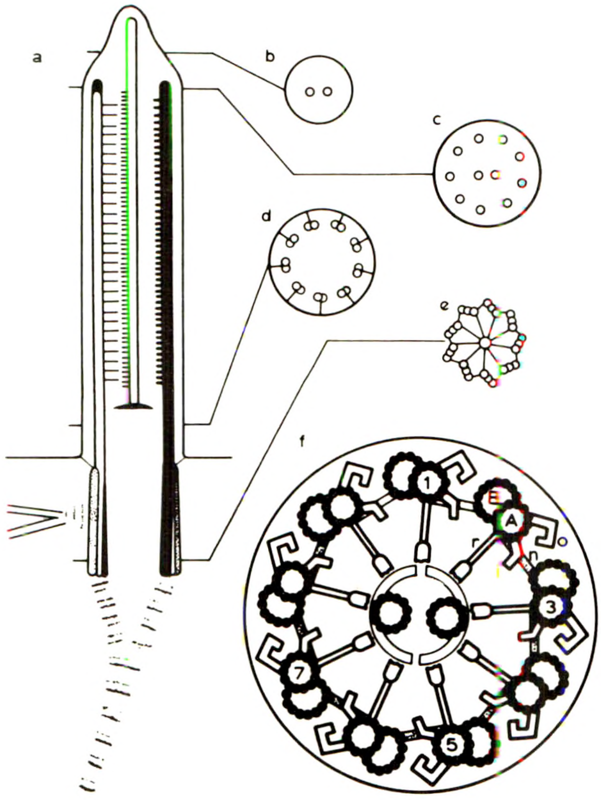

Fig 3. Diagrammatic view of longitudinal section and cross section of midportion of mammalian respiratory cilium. (Adapted from Sleigh.[6]) a — longitudinal section through ciliary shaft, basal body with attached basal foot to left, and striated root extending downward; b through e — transverse sections to show arrangement of microtubules at indicated levels, f — cross section showing microtubules (A,B) numbered clockwise as seen from basal end of cilium; o — outer dynein arms of microtubules; i — inner dynein arms of microtubules; r — radial links extending toward central complex; n — nexin links.

7. Cockayne's syndrome — deafness, dwarfism, and retinal atrophy
8. Possibly nasal acilia syndrome reported recently by Dudley et al[13]

It is not surprising that Jahrsdoerfer et al[14] have documented the existence of ultrastructural changes in the cilia of the middle ear mucosa in some cases of primary ciliary dyskinesia.

The principal concern, however, in preparing this manuscript has been to describe acquired ultramicroscopic ciliary defects.[15] Acquired ultramorphologic ciliary defects usually involve alterations or rearrangements of the 9 plus 2 microtubular pattern, in contradistinction to the dynein arm and spoke defects of genetically altered axonemes. This is shown diagrammatically in Fig 6. The ultrastructural error also may be found in the ciliary necklace, the basal bodies, or the rootlets in the many locations in which cilia are found (Fig 5). Acquired defects of the cilia are focal in location, presumably at the site of the stimulus, rather than widespread as is typical of genetic defects. In healthy individuals, some 3% to 5% of a large number of cilia examined can be shown to present alterations of the normal 9 plus 2 axoneme.[16-18] This itself may represent acquired ultrastructural alterations due to the continuous exposure of the respiratory surfaces to external environmental challenges and acquired recurrent infections, but the functional ciliary physiologic shortcoming is insufficient to produce recognizable clinical symptoms.

One of the exasperating afflictions of humans is the long-lasting common cold or upper respiratory tract infection, in which the anterior and posterior nasal discharge persists a frustratingly long time. In recent reports by Carson et al,[19] acquired nasal ciliary ultrastructural deviations were present in 22 of 30 proved natural viral colds (influenza A and B, adenovirus, parainfluenza virus, respiratory syncytial virus, and herpes simplex virus), well in excess of the 3% to 5% anticipated in healthy individuals. In the remaining eight cases, destruction of the epithelial cells by the virus had progressed too far for satisfactory observation. The ultramorphologic alterations consisted mostly of additions and deletions of the microtubules. The altered ciliary morphology was most evident after about 1 week and failed to return to normal appearance for as long as 6 to 10 weeks. The tubular alterations suggest an impaired mucociliary transport, and indeed, decreased nasal mucociliary transport has been observed experimentally in the common cold. A similar decreased nasal mucociliary transport has been observed in experimentally induced rhinovirus 44 colds.[20] Pedersen et al[21] have confirmed in part the above. Also reported is the loss of epithelial cells in the course of a cold. I would speculate that the increased and prolonged nasal discharge for several weeks following a cold is in part explained by the failure of the axoneme to return to normal configuration and hence efficient cleansing for 4 to 6 weeks or longer.

Mycoplasma pneumoniae is a bacterium[22] that deleteriously affects respiratory cilia, in this case the necklace located at the base of the shaft of the cilium. If the ciliated cells are incubated for 24 hours with a virulent form of *M pneumoniae*, there is a deterioration of the necklace. Disturbance of the necklace, which is the precursor of the cilia,[7] likely leads to alteration of the 9 plus 2 microtubule arrangement. Presumably, this occurs during the prodromal period of clinical disease. The resulting ciliary dyskinesia explains in part the clinical symptoms.

Bordetella pertussis[23] is still another bacterium that disturbs respiratory ciliary activity. In this case, the bacteria attach themselves to bases of human respiratory cilia, and this impediment leads to ciliostasis and injury and expulsion of cells. I know of no studies of the ultrastructure of such cilia.

Recently, there has been reported a functional in-

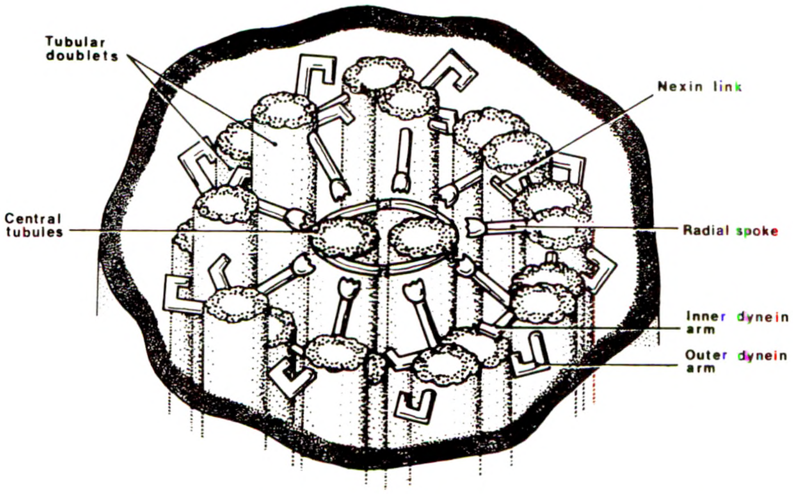

Fig 4. Three-dimensional cross-sectional view of midportion of mammalian respiratory cilium. (Adapted from Finkelstein et al.[12])

hibition of a heat-stable factor found in *Pseudomonas aeruginosa* on rabbit respiratory cilia[24] and a slowing of ciliary beat frequency of human cilia when challenged by *Hemophilus influenzae* and *P aeruginosa*.[25]

Germane to the thesis of this paper is the observation that the ciliary ultrastructure is altered when challenged by recurrent airway infections and acquired bronchiectasis.[26] In this case, alterations of dynein arms are found less frequently, and tubular abnormalities more frequently. Also found are megacilia and naked cilia. Intracytoplasmic cilia are found when the basal bodies, from which cilia axonemes extend, do not migrate to the apical cell region. In longitudinal studies, treatment of the infection caused a reduction in the percentage of observed ultrastructural abnormalities. It certainly is not clear whether the ciliary abnormalities, particularly the 9 plus 2 pattern, came first and eventu-

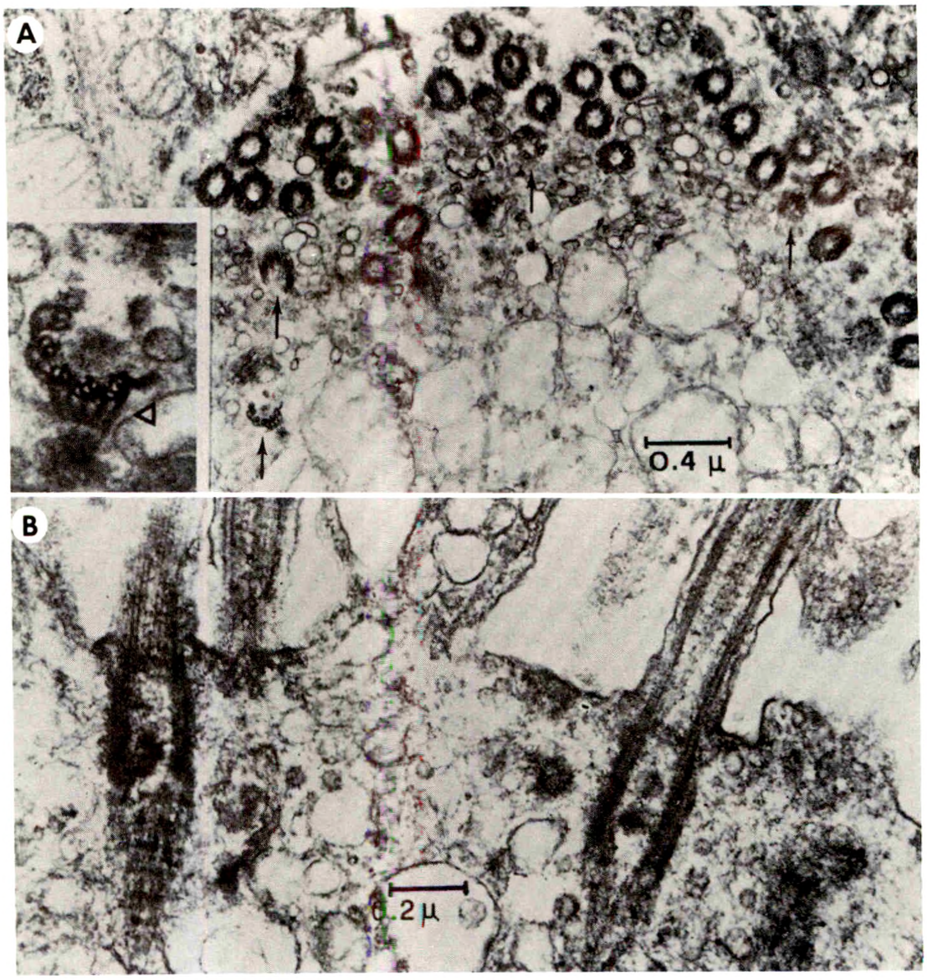

Fig 5. Ultrastructural abnormalities in cilia. A) Apical part of ciliated cell from bronchial mucosa. Note presence, among normally structured basal bodies, of so-called half-centriole (arrows). Inset: Defective basal body showing five rather than nine microtubular triplets and normal foot (arrow). (Reprinted with permission.[29]) B) Longitudinal section of basal bodies showing unusual dense granule in central core. (Reprinted with permission.[29])

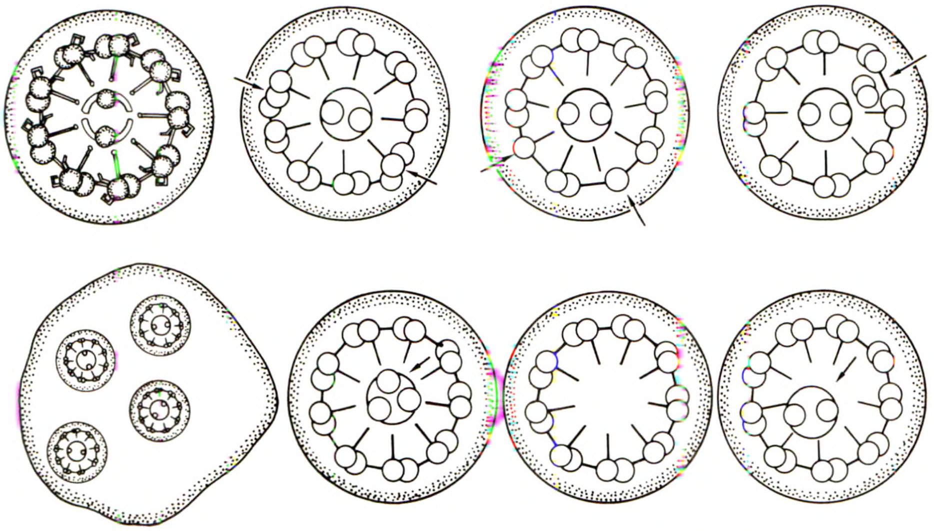

Fig 6. Abnormal alterations of ciliary axoneme. Upper left is normal. Lower left represents four axonemes in one membrane. Arrows (respectively, left to right) — triple "doublets," single "doublets," medially displaced doublet, triple central tubules, absence of central tubules, eccentric central tubules. (Adapted from Rossman et al.[16])

ated in dyskinesia, or whether the disease came first and then produced the abnormal ciliary structure. It seems likely the former was the case, since appropriate antibiotic treatment was associated with a decrease in the percentage of abnormalities. In any event, we are dealing with a fundamental aspect of the specialized cell performance and with ciliogenesis. Abnormal axonemal configurations also have been reported in the bronchi of patients suffering from tuberculosis. Whether they, too, tended to disappear following successful treatment was not made clear.

A very intriguing report concerns the association of respiratory tract cancer and morphologic alterations of the ciliary axoneme. Ailsby and Ghadially[27] reported abnormal bronchial ciliary ultrastructure from a site well away from bronchial carcinoma. Similar studies have been reported by McDowell et al.[28] During experimental respiratory carcinogenesis in animals, cytoarchitectural defects have been noted.[29] Abnormal microtubular defects have been reported from the site of an infiltrating ductal carcinoma of the postmenopausal breast.[30]

It would seem appropriate to conjecture that the ciliated cells of the upper and lower respiratory tracts, freely exposed to the external environment and the site of recurrent infections, would develop reactions to the noxious elements of this exposure. If the changes of the axoneme or those in the basal bodies, ciliary rootlets, or feet, as reported in this paper, equate with dyskinesia and mucostasis, then an opportunity for inauguration and perpetuation of disease may be at hand. An understanding of ciliogenesis, particularly in relation to inhaled environmental substances, would be a great step forward.

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EFFECTS OF ELEVATED INTRANASAL TEMPERATURE ON SUBJECTIVE AND OBJECTIVE FINDINGS IN PERENNIAL RHINITIS

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The effects of elevated intranasal temperature on symptoms and signs of perennial rhinitis were studied in 78 patients by a double-blind, randomized, placebo-controlled clinical trial. Patients were subjected to two treatments separated by a 1-week interval. Each treatment consisted of three 30-minute sessions, during which the patient's intranasal temperature was raised by inhalation of saturated hot air (42°C to 44°C). Subjective response was recorded on a daily symptom score card during the week following treatment. Nasal patency was determined before and after treatment by measuring maximal nasal expiratory and inspiratory airflow and by measuring the area covered with vapor formed by the exhaled air on a plate. Highly reproducible results were obtained by using these three objective methods. Elevation of intranasal temperature resulted in amelioration of rhinitis symptoms and in objective evidence of increased nasal patency in a significant percentage of patients compared to the placebo-treated group.

KEY WORDS — nasal airflow, nasal patency, nasal temperature, perennial rhinitis.

INTRODUCTION

Raising of intranasal temperature is reportedly effective in reducing nasal resistance.[1,2] On the other hand, exposure to cold air was found to increase nasal resistance.[1,3-5] A single clinical trial based on evaluation of symptom scores indicated that allergic rhinitis symptoms were ameliorated upon elevation of intranasal temperature.[6] The present study was undertaken in order to assess subjective patient response and to determine nasal patency by a series of objective measurements in a group of patients suffering from perennial rhinitis in whom intranasal temperature was raised for short periods of time.

MATERIALS AND METHODS

Method of Study. Intranasal temperature was raised by means of a specially designed instrument (Rhinotherm, Netzer Sereni, Israel; patent pending) from which a constant flow of saturated hot air (42°C to 44°C) was introduced into the nasal passages through two exhaust nozzles. The flow was set at 40 L/min. A placebo device, identical in appearance to the active instrument, emitted air at room temperature (20°C to 24°C). Patients selected for the study were treated with either the active or the placebo device on a double-blind, randomized basis, according to the order of their admission to the clinic. They were told that treatment was to be at different temperatures, but no preference was expressed by the experimenters for any particular temperature. Patients were instructed to breathe by inhaling through the nose and exhaling through the mouth at a normal rate. Each treatment session lasted 30 minutes, and patients were subjected to three consecutive sessions at 90-minute intervals. The entire procedure was repeated a week later. Groups were not crossed over. Patients were followed up for 1 week after each treatment. The duration of treatment sessions and the time intervals were arbitrarily selected in the design of the study. From each of the two treatment groups, 12 representative subjects were chosen on a randomized basis, and their intranasal airway temperatures during treatment were monitored using a temperature sensor (Technoterm 9300, sensor pt 100, manufactured by Testoterm, Federal Republic of Germany) installed in the nasal passages at depths of 1 and 4.5 cm from the nostrils.

Patients. This study was approved by the Kaplan Hospital Human Investigation Committee, and informed consent was obtained from all patients.

The study population consisted of 78 patients (42 males and 36 females) with an average age of 35.0 years and 33.3 years in the placebo and actively treated groups, respectively (range, 9 to 72 years in both groups). Patients were selected on the basis of a history of perennial rhinitis characterized by typical clinical manifestations of nasal congestion, itching, sneezing, and watery nasal discharge, positive skin tests to *Dermatophagoides farinae*, and elevated serum IgE antibodies (>100 IU; mean IgE

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level was 300 IU). In each case a full medical history was taken, including information on the duration of disease, other systemic diseases, previous treatments, and severity of present symptoms of rhinitis. Physical examination included anterior rhinoscopy with special attention to septal deviation, color of the mucous membranes, type of nasal discharge, and presence of nasal polyps. Skin prick tests were performed using disposable hypodermic needles according to accepted methods.

During the 2-week study period and 3 days before it, patients avoided the use of nasal decongestants, antihistamines, and corticosteroids. Asthmatic patients were instructed to continue with their routine therapy. Excluded were patients with severe nasal obstruction resulting from septal deviation or large nasal polyps, and patients who were dependent on systemic corticosteroid therapy.

Evaluation of Results. Subjective response was assessed by means of an individual daily score card on which the severity of four symptoms (sneezing, nasal blockage, discharge, and itching) was recorded by the patient according to a four-point scale with 0 for no symptoms, 1 for mild symptoms, 2 for moderate symptoms, and 3 for severe symptoms. Adverse side effects, if present, also were recorded.

Numbers on the score card were filled in by the patient on the day before treatment and once a day during the week following the treatment. A symptom index (SI) was calculated for each day by dividing the sum of the numbers recorded on that day by four (the total number of evaluated symptoms). Following treatment, the percentage change in SI relative to the pretreatment SI was calculated on each day according to the following formula:

$$\left(1-\frac{A}{B}\right) \times 100$$

where A was the SI on that day, and B was the SI before treatment.

It was elected to calculate the percentage of changes rather than presenting the actual measurements, in order to form a common basis for evaluation of results in patients with different baseline measurements. Mean duration of improvement of symptoms was calculated by counting the number of days on which improvement was reported by the patients.

Changes in nasal patency were evaluated by measuring alterations in nasal airflow by three methods.

The first method was measurement of maximal expiratory flow (MEF) by the Mini-Wright Peak Flow Meter (Airmed, Clement Clarke Ltd, London).

The second was measurement of maximal inspiratory flow (MIF) by the Youlten Peak Nasal Inspiratory Flow Meter (Clement Clarke Ltd). Measurements of MEF and MIF were recorded with an airtight face mask applied over the patient's nose and attached to the flow meter. Care was taken to avoid disturbing the nasal anatomy and to avoid air leakage. The values, expressed in L/min^{-1}, were determined as the mean of three recordings taken after the patient had become familiar with the technique and repeated recordings showed a reproducible pattern. The persons who made the measurements were not aware of which treatment the subject received. Maximal expiratory airflow through the mouth was determined by use of the Mini-Wright Peak Flow Meter without a mask. The blockage index (BI), which takes into account the effect of lower airway resistance on MEF, was calculated according to the formula of Taylor et al[7] as follows:

$$BI = \frac{\text{MEF (mouth)} - \text{MEF (nose)}}{\text{MEF (mouth)}}$$

The third method was measurement of the area covered by condensed vapor (ACV) on a polished chrome-coated plate on which arches were marked at 1-cm intervals as described by Gertner et al.[8] Values represent the mean length in centimeters of the area covered with vapor by the air exhaled from both nostrils on the metal plate. The plate was positioned horizontally under the nostrils, and the patient was instructed to breathe through the nose slowly, without force and with the mouth closed.

Measurement by all three methods was performed before the first session of treatment and immediately after the third session, in each case after blowing the nose. The same measurements were taken before and after the second treatment, a week later.

Following treatment, the percentage change in nasal patency measured by each of the above three methods was calculated according to the following formula:

$$\left(\frac{A}{B}-1\right) \times 100$$

where A was the nasal airflow value after treatment and B was the nasal airflow value before treatment.

For each method, results were tabulated in terms of the percentage change in nasal patency following treatment. The data also included cases in which treatment failed to bring about improvement.

Statistical Analysis. Experimental data obtained from the three objective methods of measurement were subjected to regression analysis in order to examine their reliability. Analysis of variance with mean separations accomplished by tests of least significant difference was carried out at p levels as indicated in the text.

RESULTS

All the patients who participated in the study had documented perennial rhinitis, with histories rang-

TABLE 1. MEAN INTRANASAL TEMPERATURES RECORDED IN REPRESENTATIVE SAMPLE OF PATIENTS AT DEPTHS OF 1 CM AND 4.5 CM FROM NOSTRIL

	Depth of Thermocouple	
Temperature of Inhaled Air (°C)	*1 cm*	*4.5 cm*
Room temperature (20-24)	32.0±0.8	34.9±1.0
Warmed air (42-44)	39.7±0.5	38.6±0.6

Values are given as means±SEM of recordings from 12 representative patients from actively treated (warmed air) group and from placebo-treated (room temperature) group. For both depths, $p < .001$ when comparing inhalation of air at room temperature with inhalation of warmed air.

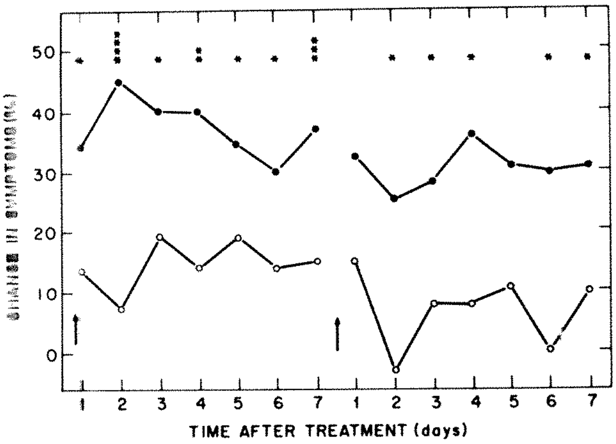
ing from 1 to 32 years. They had previously undergone conventional treatments, including antihistamine therapy, steroid sprays, sodium cromoglycate sprays, and desensitization. These treatments had been effective either temporarily or not at all. Symptoms had to be judged as sufficiently severe in order to merit admission to a clinical trial. Active treatment was administered to 44 patients (25 males and 19 females), and 34 patients (17 males and 17 females) were in the placebo group.

Table 1 records the mean intranasal temperatures measured at depths of 1 and 4.5 cm in two sample groups, each comprising 12 subjects selected at random from the actively treated group and from the placebo-treated group. As shown, the mean intranasal temperatures of subjects from the actively treated group were significantly increased, by 7.7°C and 3.7°C at depths of 1 cm and 4.5 cm, respectively.

The mean SI values prior to treatment were nearly equal in the actively treated and in the placebo-treated groups (1.28 and 1.35, respectively). The calculated symptomatic improvement (expressed in percent) during the 2 weeks of follow-up is depicted in the Figure. The rate of improvement for the whole actively treated group was 30% to 45% (mean, 37.1%) after the first treatment and 27% to 38% (mean, 32.3%) after the second treatment. The corresponding rates for the whole placebo group were 6% to 20% (mean, 14.2%) and −5% to 14% (mean, 9.9%). Symptomatic improvement was reported following the first treatment by 81.8% and 32.5% of the actively treated and placebo-treated patients, respectively; the corresponding percentages of patients that reported symptomatic improvement following the second treatment were 77.4% and 31.8%.

The mean duration of improvement in rhinitis symptoms as reported by the patients during the first week was 5.7 and 2.8 days in the actively treated and placebo-treated groups, respectively ($p < .001$); the corresponding values for the second week were 5.1 and 3.3 days ($p < .01$).

A highly significant correlation ($p < .01$) was found among the parameters measured by the three objective methods, namely, MEF, MIF, and ACV. The reproducibility of each of these methods expressed as the coefficient of variation was 95% to 99%. Since there is a direct correlation among these three methods, they seem to be reliable.



Daily changes in symptom index relative to pretreatment symptom index during each week following each treatment with active device (●) or with placebo (○). Changes are expressed in percent according to formula (in text). Arrows indicate day of treatment. Asterisks indicate significance of difference between corresponding pairs of results on each day: * — $p < .05$, ** — $p < .02$, *** — $p < .01$, **** — $p < .001$.

Mean changes in ACV following each treatment, as well as over the whole treatment period, ranged from 27.9% to 35.5% in the actively treated group, whereas little change (mean value ranging from −7.4% to 1.6%) occurred in the placebo-treated group (Table 2). Nasal patency as expressed by MIF, MEF, and BI was significantly increased as a result of the active treatment, whereas in the placebo-treated group nasal patency did not change or even deteriorated after treatment (Table 2). The percentage of patients in whom nasal patency in terms of ACV, MIF, and MEF improved after treatment was 60.0% to 84.0% (mean, 78.2%) in the actively treated group and 8.3% to 25.0% (mean, 14.4%) in the placebo-treated group. No significant difference in the patients' response to treatment was observed with respect to age, sex, baseline symptoms, or pretreatment IgE levels.

No side effects were noted during either treatment or follow-up. All patients found the method of delivery of saturated hot air to be acceptable. The rates of dropouts were 16.7% and 20.7% from the actively treated and placebo-treated groups, respectively.

DISCUSSION

The validity of methods used in the past to assess nasal reaction in terms of subjective patient response[9,10] or by measurement of mucus production[11-13] is questionable, since they are dependent on patient compliance, their reproducibility is poor, and the interpretation of the results is unclear. In cases in which the effects of various stimuli or drugs are to be assessed, it is imperative to sup-

TABLE 2. CHANGES IN PERCENT IN ACV, MIF, MEF, AND BI, FOLLOWING INTRANASAL TEMPERATURE ELEVATION

	ACV		*MIF*		*MEF*		*BI*	
	Placebo	*Active*	*Placebo*	*Active*	*Placebo*	*Active*	*Placebo*	*Active*
After versus before treatment 1	1.6*	29.9	− 9.5†	38.1	5.3*	34.5	−12.7†	16.0
After versus before treatment 2	−7.4*	27.9	− 5.6†	29.1	0.1†	25.5	− 7.6	11.6
After treatment 2 versus before treatment 1	1.4*	35.5	−14.0†	36.3	−18.6§	36.7	4.2†	24.9

Negative values indicate decrease in nasal patency. Statistical significance determined by comparing values of placebo and active treatments for each single measurement method.

ACV — area covered by vapor, MIF — maximal inspiratory flow, MEF — maximal expiratory flow, BI — blockage index.

*$p < .001$.

†$p < .01$.

§$p < .05$.

plement the use of symptom scores, as a clinical parameter for evaluating the magnitude of patient response, by objective and quantitative methods.

Blockage of the nose is the symptom most commonly used for objective assessment. Nasal patency can be investigated by means of rhinomanometry.[14] In this study, however, we employed the simpler measurements of MEF and MIF, both of which have proved to be of clinical and scientific value in the evaluation of changes in nasal patency.[1,7,15-21] The third method involves measuring the ACV formed by the exhaled nasal airflow that condenses on a metal plate. To the best of our knowledge, this is the first time that this recently described method has been employed in a clinical trial. These three methods of measurement proved to be clinically applicable for the following reasons: they are simple to use; they do not interfere with the anatomy of the nose and the physiologic airflow is thus maintained; they are comfortable for the patient; and — most important — once the patient has learned the technique following a brief period of instruction and exercise, the results are reliable and reproducible.

Perennial rhinitis is a chronic condition in which a psychic factor is present, since its management involves the prolonged use of drugs that often cease to provide adequate relief. It is thus possible that a placebo effect[22] may account for the high rate of improvement reported by the placebo-treated patients.

The objective tests used in this study, however, demonstrated a much more highly significant difference between the therapeutic activity of the active device and that of the placebo with regard to nasal patency. Following treatment, increased nasal patency was observed in 78.2% of the actively treated patients, as compared with only 14.4% of the placebo-treated group. Moreover, many of the placebo-treated patients showed a decreased nasal patency after treatment, as reflected in the negative values recorded in Table 2. Also, after the second treatment, placebo-treated patients reported less symptomatic improvement as compared to the actively treated patients and to the first treatment.

The pathogenetic process of allergic rhinitis is thought to commence with the formation of IgE antibodies as a result of exposure to an antigen. These antibodies bind to receptors on mast cells and basophils. Subsequent exposure to the antigen causes cross-linking of specific IgE antibodies to these cells with the release of inflammatory mediators. The mediators interact with neural elements, mucosal glands, and blood vessels to cause sneezing, rhinorrhea, and nasal congestion, which represent the major physiologic responses associated with allergic rhinitis.[23,24] The mechanism whereby heat exerts its effect on nasal mucosa is unknown. This may include a direct effect on the capacitance vessels or on mucosal glands; however, recent work has raised the possibility that a metabolic process also may be involved. Togias et al[25] showed that patients react to nasal challenge with cold air with nasal stuffiness and hypersecretion accompanied by the appearance of inflammatory mediators in nasal secretion. It has been postulated that mast cells are temperature-sensitive and that cooling of the airway leads to mast cell degranulation.[26] Heat-induced changes in the release of mast cell mediators may be responsible for the relief from nasal symptoms experienced by our patients. This inhibitory effect is currently being explored in our laboratory.

The normal intranasal temperature varies between 31°C at the nares and 36°C at the choanae.[27] This temperature gradient contributes to the conditioning of the inspired air and the recovery of heat and water from the expired air. Our recordings (Table 1) show that in the placebo-treated patients, intranasal temperature was kept within normal limits. In the actively treated patients, it was possible by supplying air under controlled conditions of flow, temperature, and saturation to overcome the conditioning ability of the nasal passages and hence to increase the intranasal temperature throughout treatment. The role of moisture in the beneficial effect of the treatment was not determined in this study.

The Figure compares the average symptomatic effect during the follow-up period of the active treatment with that of the placebo. It is evident that the subjectively perceived effect of treatment is superior in the actively treated group. Comparison between the effects of treatment during the first and second weeks shows a reproducible pattern, thus further lending credibility to the effectiveness of treatment. Evidently, the second treatment had no additional effect on SI.

The amelioration of nasal symptoms and the increase in nasal patency observed in patients exposed to saturated hot air may have a clinical application in providing symptomatic relief in perennial rhinitis.

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COMPARISON OF THE INTRASUBJECT REPEATABILITY OF AUDITORY BRAIN STEM AND MIDDLE LATENCY RESPONSES ELICITED IN YOUNG CHILDREN

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The auditory brain stem response (ABR) and middle latency response (MLR) were studied in 48 young children (96 ears). The responses were elicited using low intensity stimuli (30-dB nHL clicks) and simultaneously were recorded on a dual time base. Both the ABR and MLR were elicited in 70 ears. In 12 ears, just one response was recorded (ABR in eight ears and the MLR in four ears). In 14 ears, neither response was recorded. Test-retest analysis on the same subject demonstrated that the ABR was more repeatable and easier to identify than the MLR. The test-retest difference was determined for the amplitude and latency of the ABR and MLR waveforms. The test-retest latency difference for wave Pa was found to be 3.6 times larger than for wave V. The normalized test-retest amplitude difference for Pϕ-Na, Na-Pa, and Pa-Nb was found to be two to three times larger than for wave V. These data support the conclusion that the ABR, rather than the MLR, should be used to measure hearing in young children. The authors also advocate using minimal high pass (HP) filtering when recording the ABR in a sedated or sleeping child. Muscle artifact was not found to be a problem. The authors suggest the use of minimal HP filtering so that phase-shift distortion is minimized and a larger response amplitude can be recorded.

KEY WORDS — auditory brain stem response, intrasubject repeatability, middle latency response, test-retest analysis, threshold determination.

INTRODUCTION

One of the most important applications of auditory evoked potential (AEP) testing is the evaluation of hearing in neonates and young children. At the University of Tennessee's Newborn Center, all infants who are placed on the high risk registry are evaluated initially with a Crib-o-gram and then referred (regardless of Crib-o-gram result) for AEP testing at 4 months post–full term (13 months conceptional age). Ideally, all infants should be tested with AEP before they leave the newborn center; however, the availability of equipment and personnel, along with limited funds available to service an indigent population, have prohibited this in our study. The cost-effectiveness of auditory brain stem response (ABR) versus Crib-o-gram testing of newborns is still debated, without clear results.[1] Both tests appear to have high positive rates. Middle ear effusions are common in this age group and are responsible for 52.8%[1] to 61.9%[2] of the positive results. Because of the transient nature of many ABR abnormalities found in the newborn, follow-up evaluation is considered mandatory.[3]

The goal of auditory evaluation of infants is to detect and habilitate hearing losses in children before 6 months of age.[4] In our protocol, referral for AEP testing was done when a child was 4 months of age (13 months conceptional age). The age of the child at the time of testing is an important factor. Zimmerman et al[5] have shown that the ABR undergoes dramatic changes in the first 2 weeks of life of a full-term infant. As the subject's age increases, the ABR slowly approximates the adult's. Alberti et al[2] demonstrated that follow-up testing of children over 3 months of age has a lower failure rate than studies performed on newborns. Auditory habilitation still can be initiated after follow-up testing and completed before the child is 6 months of age. Screening AEP protocols often use a 30- to 40-dB nHL click stimulus,[1,4] and children that have an ABR threshold above 40 dB are referred for auditory habilitation.

In our AEP testing protocol, ABR and the middle latency response (MLR) are recorded simultaneously on a dual time base. There has been much debate in the literature as to which response is the best predictor of hearing sensitivity in the newborn.[6] Early researchers who have used steeply sloping analog filters have reported recording the MLR reliably in children; however, recent studies using gradually sloping filters have found the MLR to be recorded unreliably.[7] It is the purpose of this paper to compare the ABR and MLR elicited from young children and to confirm or refute the reported difficulty in recording the MLR in this subject population. The ability to record each response with a near-threshold stimulus will be determined by documenting its test-retest repeatability. An argument will be made that the response with the smallest test-retest difference will be more repeatable and thus more recognizable by an observer as a true response. It therefore will be the more accurate measurement of hearing.

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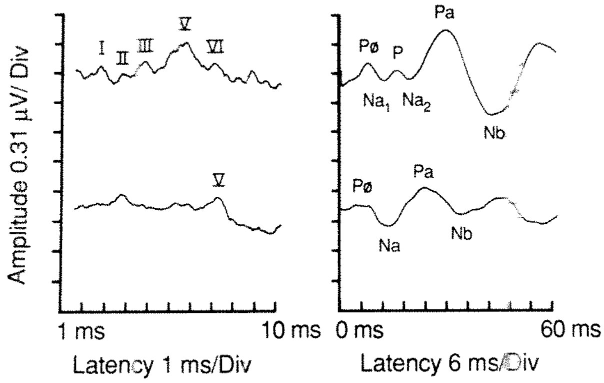

Method used in waveform labeling. Top waveforms are from adult presented with 70-dB nHL stimulus. Bottom waveforms are from infant presented with 30-dB nHL stimulus.

METHODS

Subjects. Forty-eight children under the age of 13 months were evaluated by the University of Tennessee AEP Laboratory over a 12-month period. No child was sedated. The mean age was 8.0 months, with a standard deviation of 2.7 months and a range of 1 to 12 months. The vast majority of children were referred from the University of Tennessee–Memphis Newborn Center. Most of these children were identified as being at risk for hearing loss because of low birth weight. One of the children had Down's syndrome; the rest had no neurologic diagnoses. All children had normal results on otologic examination. Comparisons of the ABR and MLR were made in 42 children (82 ears) who had an AEP recorded (ABR and/or MLR) at 30 dB nHL. Ears with a threshold of greater than 30 dB nHL were not evaluated, since below-threshold recordings will have a high and equal variability for both test conditions.

Equipment. The Pathfinder II (Nicolet Corp) was used to record the ABR and MLR simultaneously on a dual time base. The stimuli were 70- and 30-dB nHL 0.1-ms rarefaction clicks presented at a rate of 9.7/s through TDH-49 headphones housed in Mx-41 cushions. Zero decibels nHL equals 39 dB pe SPL (peak equivalent sound pressure level). If no AEPs were recorded with the 30-dB nHL stimuli, then the stimulus intensity was increased in 10-dB nHL increments until threshold was found. The time base was 10 ms for the ABR and 60 ms for the MLR. Recording filters were 15 to 3,000 Hz for the ABR and 15 to 250 Hz for the MLR (Butterworth filters with 12-dB/octave slopes). All waveforms represented an average of 1,000 stimulus presentations. No subject was sedated; most were tested during natural sleep; and all were tested in a Tracoustic model RS-255A soundproof booth.

Waveform Identification. A response was considered valid in this study if identified in two of two recordings. If the waveform was seen only once in the two averages, additional responses were recorded. Analysis of the waveforms recorded from the 70-dB nHL data and the additional 30-dB nHL recordings was used clinically to determine if the waveforms were present. Only the first two recordings, however, were considered in the test-retest analysis. A subject was considered to pass the auditory testing if either an ABR or MLR was present at 30 dB nHL. If the subject had a 40-dB threshold, then the result was considered to be borderline. Thresholds greater than 40 dB were considered abnormal.

Data Analysis. Waveform repeatability was determined by analyzing the waveform pairs presented to each subject. If more than two waveforms were recorded, then the first two waves were analyzed. If no response was identified for either ABR or MLR, a best-guess measurement was taken. If the presenting stimulus was below the subject's threshold (neither the ABR nor the MLR could be identified), then the ear was eliminated from analysis. The waveforms were labeled according to Kavanagh and Domico.[8] Wave Pϕ was identified as the slow component of the ABR, and wave Na was identified as the lowest trough between wave Pϕ and wave Pa (Na1 or Na2, whichever was lower; see Figure). The latency and amplitude of wave V were recorded for the ABR. The latency for waves Pϕ and Pa, along with the Pϕ-Na, Na-Pa, and Pa-Nb amplitudes, was recorded for the MLR. In a few waveforms, Nb and the trough after wave V had a latency longer than the time base. In this situation, the data point at the end of the time base was used for statistical analysis. All waveforms were measured by the same observer. There is no statistical advantage to having more than one observer for the type of analysis used in this study.

Latency data were recorded on a different scale (time base) for ABR and MLR. The wave latency difference in the wave pairs was corrected for scaling errors for waves V (10-ms time base) and Pϕ (60-ms time base) by the following equation:

$$\text{Latency difference} = \text{ABS}(A - B)/10 \text{ ms}$$

where ABS is the absolute value, A is the recording from the first waveform, and B is the recording from the second waveform.

The wave latency difference for waves Pϕ (60-ms time base) and Pa (60-ms time base) was corrected for scaling errors by the following equation:

$$\text{Latency difference} = \text{ABS}(A - B)/60 \text{ ms}$$

where ABS is the absolute value, A is the recording from the first waveform, and B is the recording from the second waveform.

Latency data were not normalized, since the magnitude of this parameter has little effect on wave peak identifiability, only on location.

TABLE 1. TEST-RETEST DIFFERENCES OF WAVE LATENCY (PERCENT CHANGE OF WAVE PEAK IN RELATION TO LENGTH OF TIME BASE)

Wave Peak	*Time Base* (Weight Factor) (ms)*	*Mean**	*Standard Deviation**	*Variance**	*Significance† Wave V vs MLR*	*Variance-Ratio (Larger/Smaller)*
V	10	1.7%	1.94%	3.75%		
Pϕ (V)	10	5.8%	3.55%	30.69%	p<.0001	8.18
Pϕ (V)	60	1.0%	0.92%	0.85%	p<.0001	4.41
Pa	60	6.2%	6.02%	36.18%	p<.0011	9.64

*Scaled by equation: Scaled data = [ABS(A − B)/weight factor] x 100%, where ABS is absolute value, A is first observation, and B is second observation. Weight factor is equal to time base.

†Two-tailed paired *t* test used to calculate significance on means and standard deviation from analysis of variance.

The amplitude difference for all wave slopes (ABR and MLR) was normalized to 1.0. This correction was done because amplitude does affect peak identifiability. For example, a 0.2-μV variation will affect the identification of wave V more than Pa, because Pa is a much larger waveform. The normalization of the data will allow equal weight to be given to a 50% reduction in wave amplitude (regardless of the average wave amplitude). Scaling errors did not exist, because the vertical scale for the ABR and MLR recordings was the same. Normalization was performed by an equation similar to the one used to determine unilateral hypoactivity during electronystagmographic testing.[9]

$$\text{Amplitude difference} = \text{ABS}(A - B)/A + B$$

where ABS is the absolute value, A is the recording from the first waveform, and B is the recording from the second waveform.

Means for the scaled latency difference and the normalized amplitude difference underwent statistical analysis using analysis of variance and *t* tests. The variances of these parameters also were compared using the F-max test. Since 82 data points were recorded for each condition, a ratio in variances greater than 1.7 will denote a significant difference with $p < .01$ (Tables 1 and 2). Because the *t* and F-max tests were significant, the data were examined more closely to determine underlying explanations for these differences.

Reliability of a clinical procedure or instrument is defined as the correlation between measurements repeated on the same subject.[10] Intrasubject correlations were calculated for the ABR and MLR from variance component estimates obtained from analyses of variance.[11] After transformation, differences in reliability of latency and amplitude differences for the ABR and MLR were tested with a two-tailed paired *t* test.[12]

Data reliability is related to the variances of the test-retest differences in the two data sets.

$$\text{Reliability} = R_{12} \text{ (correlation between } Y_1 \text{ and } Y_2\text{)}$$
$$\text{Var}[Y_1 - Y_2] = \text{Var}[Y_1] + \text{Var}[Y_2] - (2R_{12} \times (\text{Var}[Y_1])^{1/2} \times (\text{Var}[Y_2])^{1/2})$$

where Y_1 is the first data set, Y_2 is the second data set, and Var is the variance.

Only the variance due to retesting and not due to the different patients or different ears was evaluated. We estimated R_{12} by an intraclass correlation formula. (This refers to the correlation between repeated measurements recorded within ears on the same patient.)

$$R_{12} = \frac{S_p^2 + S_{e/p}^2}{S_p^2 + S_{e/p}^2 + S_e^2}$$

where S^2 is the variance of the entire data set, p is the patient variance, e is the test-retest variance (error), and e/p is the variance of ears within patients.

RESULTS

In the 48 subjects (96 ears) who were tested, 82 ears had an AEP response recorded (ABR or MLR) at 30 dB nHL, four ears had an AEP threshold of 40 dB nHL, nine ears had a threshold above 40 dB nHL, and one ear was not tested because the subject awoke (Table 3). A response had to be identified in both initial waveforms to be considered valid. The ABR was not identified in four of 82 test ears (4.9%), and wave Pa of the MLR was not identified in eight of 82 test ears (9.7%). This was not a significant difference (χ^2 test, $p > .2$). For the 164

TABLE 2. TEST-RETEST DIFFERENCES OF WAVE AMPLITUDE (DATA NORMALIZED)

Wave Slope	*Time Base (ms)*	*Mean**	*Standard Deviation**	*Variance**	*Significance† V Amplitude vs MLR*	*Variance Ratio (MLR Slope/V Amplitude; Larger/Smaller)*
V amplitude	10	12.6%	12.2%	149%		
Pϕ (V)-Na	60	25.0%	20.6%	426%	p<.0001	2.86
Na-Pa	60	26.8%	19.6%	386%	p<.0001	2.59
Pa-Nb	60	29.9%	21.7%	469%	p<.0001	3.15

*Normalized by equation: Normalized data = [ABS(A − B)/A + B] x 100%, where ABS is absolute value, A is first observation, and B is second observation.

†Two-tailed paired *t* test used to calculate significance on means and standard deviation from analysis of variance.

TABLE 3. ABSENCE OF EITHER ABR OR MLR AT 30 dB nHL

	*Responses (ABR or MLR) Present in 2 of 2 Recordings**	*One Response (ABR or MLR) Absent in 1 of 2 Recordings†*	*One Response (ABR or MLR) Absent in 2 of 2 Recordings†*
ABR	79/82	0	3
MLR	74/82	6	2

Does not include ears in which no response could be identified.

*All responses identified.

†One response not identified.

TABLE 4. SUBJECT LATENCY AND AMPLITUDE DATA FOR 30-dB nHL CLICK STIMULUS

	Latency (ms)		*Amplitude (μV)*	
	Mean	*SD*	*Mean*	*SD*
Wave V	7.34	0.53	0.27	0.11
Pϕ	8.70	0.97		
Pa	28.79	6.13		
Pϕ-Na			0.29	0.15
Na-Pa			0.43	0.24
Pa-Nb			0.29	0.24

Forty-two subjects; mean age, 8.0 months, and SD, 2.8 months.

waveforms (82 waveform pairs), wave V was not identified in seven (4.3%), wave Pϕ in two (1.2%), and wave Pa in ten (6.1%). In three of our subjects (six waveforms), wave V was not recorded when wave Pϕ was. Three possible explanations exist for this occurrence: 1) the high frequency energy in the first time base obscured the response; 2) the scaling differences of the time base obscured the response (the down slope of wave V on the shorter time base will not be as steep and, thus, not be as visible); or 3) the shorter time base missed the response.

Because there are three differences in the recording techniques used, it is impossible to tell with certainty which had the greatest effect; however, it is our belief that the last explanation was not the major factor. The mean latency of wave V was equal to 7.34 ms (standard deviation, 0.53 ms), and the latency of wave Pϕ was approximately 1.4 ms longer than that of wave V (this is due to the phase shifting of analog filters) (Table 4). In two subjects who had no identifiable wave V, wave Pϕ's latency was less than 9.8 ms. In the third subject, the latency of wave Pϕ was prolonged, but additional recordings identified wave V at 7.83 ms. Thus, the absence of a recorded wave V in these subjects was not solely related to the length of the ABR time base.

The determination of the presence or absence of a response in these waveforms was a subjective decision and underscores the value of using the test-retest latency and amplitude difference as a method for comparing response identifiability.

TEST-RETEST DIFFERENCES OF SCALED LATENCY AND NORMALIZED AMPLITUDE DATA

Data Repeatability. Statistical analysis was performed after correction for possible scaling errors in latency data and after normalization of the amplitude data. The scaled latency difference for wave Pa was 3.6 times greater than that seen for wave V ($p < .0001$) (Table 1). If scaling differences were not corrected, this comparison would be even more significant. Wave Pϕ (recorded on the 60-ms time base) was also less repeatable than wave V (recorded on the 10-ms time base) if no adjustment for time base scale was made ($p < .0001$). Wave Pϕ was more repeatable than wave V if an adjustment for scaling differences was made ($p < .0011$) (Table 1). The same pattern was observed for variance ratios; all differences were significant.

The wave V amplitude was two to three times more repeatable than the slopes of Pϕ-Na, Na-Pa, and Pa-Nb (Table 2). Wave V differed by an average of 12%, whereas the MLR waveforms differed from 25% to 30%. The test-retest Pϕ-Na amplitude difference was 1.98 times greater than the wave V amplitude difference ($p < .0001$), the Na-Pa amplitude difference was 2.13 times greater than the wave V amplitude difference ($p < .0001$), and the Pa-Nb amplitude difference was 2.37 times greater than the wave V amplitude difference ($p < .0001$).

Data Reliability. The reliability of the ABR (wave V) latency difference was found to be significantly greater ($p < .0001$) than those estimated for MLR (waves Pϕ and Pa) latency differences. There were no significant differences shown between the reliabilities of amplitude differences for the ABR and MLR (Table 5).

Latency and Amplitude Data. The mean latency and amplitude data for the group of subjects are presented in Table 4. As expected, latency values

TABLE 5. INTRASUBJECT RELIABILITY OF LATENCY AND AMPLITUDE MEASUREMENTS

	Wave Peak (Latency)			*Wave Slope (Amplitude)*			
	V	*Pϕ*	*Pa*	*V Amplitude*	*Pϕ-Na*	*Na-Pa*	*Pa-Nb*
Variance components (percent variation)							
Subject	0.184(67.7)	0.290(3.1)	8.45(22.3)	0.004(28.4)	0.007(31.2)	0.012(21.0)	0.000(0.0)
Ear/subject	0.067(23.4)	0.590(62.8)	15.96(42.2)	0.003(19.7)	0.003(12.0)	15.960(21.9)	0.025(43.0)
Test-retest	0.034(11.8)	0.321(34.1)	13.40(35.5)	0.007(51.9)	0.013(56.8)	13.400(57.1)	0.034(57.0)
Reliability	88.20	65.90	64.50	48.10	43.20	42.90	43.00
Z transformation*	1.38	0.79	0.77	0.53	0.46	0.46	0.46
Significance Wave V vs MLR		$p < .0001$	$p < .0001$		$p < .13$	$p < .13$	$p < .13$

*Standard deviation $= \sqrt{\frac{1}{n-3} + \frac{1}{n-3}}$ where n = 164.

TABLE 6. FILTERING PARAMETERS USED BY INVESTIGATORS TO EVALUATE HEARING IN YOUNG CHILDREN

Author	Band Pass (Hz)	Slope (dB/octave)
Bradford et al[13]	250-3,200	6
	100-2,000	6
Cornacchia et al[14]	250-1,600	
Dennis et al[15]	100-3,000	12 or 24*
	150-3,000	12†
Despland and Galambos[16]	150-3,000	12†
Goldstein et al[17]	100-3,000	
Fawer et al[18]	250-1,600	
Harris et al[19]	250-3,200	
Hecox and Galambos[20]	80-3,000	
Kileny[21]	150-3,000	12†
Lary et al[22]	300-3,000	
Levi et al[23]	250-5,000	
Mendelson et al[24]	100-3,000	
Mjoen[25]	150-4,500	
Mochizuki et al[26]	80-1,200	
Mokotoff et al[27]	100-3,000	
Orlowski et al[28]	150-3,000	12†
Paludetti et al[29]	250-3,000	
Rotteveel et al[30]	30-3,000	12
Schulman-Galambos and Galambos[31]	150-1,500	12†
Shimizu et al[1]	100-3,000	
Stockard et al[32]	100-3,000	
Zubick et al[33]	150-3,000	

*Authors used Pathfinder II by Nicolet.

†Assumed by fact that researchers used CA-1000 by Nicolet.

are slightly prolonged compared to those for normal subjects.

DISCUSSION

Experimental Design. Experimental studies comparing the efficacy of MLR and ABR in predicting auditory sensitivity have for the most part compared response threshold. The response with the lowest threshold is felt to be the more predictive of the true behavioral threshold. This experimental design has two drawbacks. First, it requires multiple recordings to find threshold. Second, it requires a subjective judgment to identify the presence or absence of a waveform. In our report, data were generated not only on the presence or absence of the waveform (Table 3), but also on the repeatability of the waveform. It is reasoned that waveforms that are more repeatable will be more identifiable and thus a more desirable parameter to measure. Repeatability of the waveforms elicited by a low intensity stimulus can be measured objectively by determining the test-retest differences among the various waveforms recorded from each subject. Except for the determination of complete absence of all response, the observer does not have to make a judgment about the presence or absence of individual waveforms. If a response (both ABR and MLR) was absent (subthreshold), neither the ABR nor the MLR was analyzed. The incorrect identification of data as subthreshold that actually contained a very poorly defined response will not bias the variability comparisons in the remainder of the data. Any data that contained a well-defined waveform (either ABR or MLR) were analyzed. If only one waveform was identified (for example, ABR) and the other was absent (for example, MLR), then a best-guess measurement is made for the absent waveform. In a recording with no response, it would be possible for the observer to measure either latency or amplitude so that it equaled the expected value; however, it is very unlikely that both of these parameters could be made equal to that found in a true waveform.

The use of intrasubject test-retest differences in order to determine the identifiability of AEPs has not been reported previously in the literature. A decrease in waveform repeatability can be created by both subject factors (eg, level of arousal) and background noise. Subject factors are most important when recording the MLR (waves Na, Pa, and Pb). These factors were kept to a minimum by recording the ABR and MLR simultaneously on a dual time base, and by recording the waveform pairs in a relatively short period of time. Another major cause of decreased repeatability is background noise. It can be argued that an increase in variability will correspond to a decrease in signal-to-noise ratio. Variability also will hinder the identification of an absent response. In other words, it is easier to identify an absent response if each waveform in the pair has the same flat configuration, rather than an undulating baseline caused by background noise. Whether waveform variations are caused by subject factors or noise, they will cause the waveforms to be less repeatable and thus affect identification.

The two parameters that can be measured are latency and amplitude. The variability of these measurements can be determined by a number of methods. We chose to normalize all amplitude differences so that a 50% reduction in waveform amplitude would have an equal effect on waveform variability regardless of the height of the complex. Latency measurements were scaled by dividing the latency difference in the waveform pairs by the length of the time base. This was done because the change in peak position apparent to the examiner is dependent upon the scale of the digitized waveform. Thus, a 5-ms latency change will have less of an observable effect on a 60-ms time base than on a 10-ms time base. As a control, wave Pφ was scaled for both a 10- and a 60-ms time base. If no correction for the time base scale was done, the difference in variability between wave V of the ABR and wave Pa of the MLR would be more pronounced than shown in Table 1.

The variability for latency was much greater than that found for amplitude. This is to be expected, since the observer tended to search more for an amplitude deflection that approximated the expected waveform than for a particular position (latency).

TABLE 7. PARAMETERS FOR RECORDING OF MLR IN CHILDREN

Author	*Filter Slope (dB/octave)*	*Band Pass (Hz)*	*Stimulus (dB)*	*Number, Age*	*Result*
Wolf and Goldstein[41]	48	25-75	30 10	5, 1-4 d 5, 1-4 d	MLR recorded in all subjects MLR recorded in 3 of 5 subjects
Wolf and Goldstein[42]	48	25-85	10, 30, 50	20, 1-4 d	Composite MLR from all subjects recorded
McRandle et al[43]		20-125	55	10, 1-3 d	MLR recorded in all subjects
Frye-Osier et al[44]	48	25-85	20, 40, 60	13, 1-7 d	As a group had MLRs down to 20 dB
Mendel et al[46]	24 24	10-500* 25-175*	30, 45	18, 1-8 mo	76% of MLRs present at 30 dB nHL 94% of MLRs present at 45 dB nHL
Mendelson and Salamy[45]	24	20-175	60	15, premature 15, term 15, 3-4 yr	MLR can be recorded reliably in newborns, and waveforms in term infants are similar to those in adults
Suzuki et al[47]	Digital Digital	HP 20 HP 30	60 60	26, 1-7 yr 26, 1-7 yr	83% had detectable Pa; none had detectable Pb <40% had detectable Pa; none had detectable Pb
Engel[38]			72	24, 0-5 d	MLRs in only 8 of 24 newborns
Okitsu[37]	18	30-300	30, 40, 50	20, 0.3-3.3 yr	Pa in 29% at 30 dB nHL (sleeping); Pa in 36% at 40 dB nHL (sleeping)
	6	20-300	50	20, 0.3-3.3 yr	No significant difference from the 30-300 Hz, 18 dB/octave condition
Hirabayashi[40]		0.5-3,000	20, 40, 60	37, <2-7 yr	Pa in infants and younger children very unstable
Rotteveel et al[30]	12	5-250	70	25, birth 25, 3 mo	Pa and Nb "hardly recognizable"; Pa and Nb identified in group averages

HP — high pass.
*Cascading filters.

Filtering Parameters and Stimulus Intensity Level. The band pass filter used to record the MLR in this study approximates that used by many laboratories. The filtering for the ABR (15 to 3,000 Hz), however, differs from that used in most clinical trials (Table 6).[1,13-33] By setting the high pass (HP) filter to 15 Hz (instead of 100 to 150 Hz), phase shift distortion of the waveform is minimized and response amplitude will be larger.[8,34] The use of minimal HP filtering has been advocated by researchers,[35] but has not found widespread clinical use. In our study, the use of an open filter setting for the ABR resulted in the recording of both wave V and the slow component (Pφ) on the 10-ms timebase.

Although HP analog filtration of the ABR (100 to 150 Hz) causes phase shift distortion,[36] it also eliminates muscle artifact and thus may be beneficial in the adult subject. In a sedated or sleeping young child, however, muscle artifact is not a major factor. No child (less than 13 months of age) evaluated in our protocol (using a band pass of 15 to 3,000 Hz) was sedated. In only one of the 48 children did we have to suspend testing in one ear because the child awoke. It is doubtful that using an HP filter of 150 Hz in this child would have allowed the recording of a response, since once the subject awoke the major concern was not muscle artifact, but preserving the electrodes. In an awake cooperative child in whom muscle artifact is a problem, however, HP filtration may be beneficial.

It should be remembered that the lowest discernible frequency when recording with a 10-ms time base is 100 Hz (1/time base). Frequencies below this value will tend to induce a baseline shift, since their wavelengths are longer than the recording time base. Baseline correction can be used to eliminate this shift. Thus, even though the same analog filtering was used on the two time bases in our study, activity below 100 Hz will not be recorded as well on the 10-ms time base as on the 60-ms time base. The major effect that HP filters have on the ABR is one of phase shift distortion. Filters phase-shift frequencies that they pass. Thus, to avoid undesirable phase shift distortions, the cut-off frequency of the filter should be several octaves below the major frequency of the response.

The click intensity level in our screening protocol was set at 30 dB nHL. Only 5% of the ears (four of 86) that did not have an AEP response at 30 dB nHL had one at 40 dB nHL. This is similar to the 6% value found by Alberti et al[2] in follow-up AEP testing.

Analysis of Test-Retest Repeatability Data. Researchers are divided on whether ABR or MLR is best for the evaluation of hearing of newborns and young children. Many researchers have found the MLR to be recorded inconsistently in this population,[37-40] while others advocate its use.[41-46] Musiek et al[6] and Suzuki et al[47] felt that the differences in the various research results may be due to the filter slopes used to record data. They observed that laboratories that reliably recorded the MLR used steeply sloping filters (≥24 dB/octave) and those that did not reliably record the MLR used gradually sloping filters (≤6 dB/octave). Scherg[48] and Suzuki et al[49] demonstrated that steeply sloping filters will phase-shift the response with a resultant decrease in amplitude wave Pφ[49] and an augmentation of waves

Nb and Pb.[48,49] Kavanagh and Domico[8] also recorded this effect and noted that although the MLR was augmented, the intersubject variability of normative values also increased. Thus, the augmentation caused by phase shifting may not be desirable. While there is agreement that wave Pb is not recorded reliably with gradually sloping filters in young children, there is much confusion regarding the recordability of wave Pa. Suzuki et al,[47] using 60-dB stimuli, found that wave Pa was recorded in 83% of children 1 to 7 years of age. Hirabayashi[40] describes wave Pa to be very unstable in infants and young children; and Okitsu[37] recorded wave Pa in only 29% of sleeping children 0.3 to 3.3 years of age who were presented with a 30-dB click. Some of the differences in these results may be explained by the high test-retest variability of the MLR and the differences in criteria used by observers to judge the presence or absence of a response.

High pass filtering is also an important variable, since HP filters above 20 Hz (digital filter) have been shown to reduce wave Pa's detectability in children to below 40%.[47,49] Thus, authors using HP filters with cutoff frequencies above 20 to 30 Hz may be eliminating the biologic response. Table 7[30,37,38,40-47] summarizes various reports pertaining to the use of MLR in the evaluation of hearing in young children.

The phase shifting by our filters could have created an augmented wave Pa. This would tend to bias the study toward showing a more repeatable MLR. Nevertheless, our data still showed wave Pa to be less repeatable and thus harder to identify than wave V of the ABR.

The age of the child is also an important variable, because the ABR rapidly changes up to 1 month (post-full term).[5] It then enters a phase in which it slowly approaches normal adult values over the next 1.5 to 4 years. Our children were all in this second phase of maturation. Thus, the variability of the evoked response may be even more profound in the newborn infant (≤1 month), whose auditory system is undergoing rapid maturation. This was demonstrated by Rotteveel et al,[30] who studied longitudinally the MLR for 25 subjects at birth and at 3 months of age. They found that waves Pa and Nb were "hardly recognizable" in term infants but were "seen" at 3 months of age.

Analysis of Variance: Variability due to Ears and Patients. Waves P0 and Pa also were found to have a greater variation between ears than between subjects (Table 5). This is an unexpected finding, since stimulus and subject parameters were the same in all test conditions. The testing order of the ears was not randomized. The two left data sets usually were collected first. This gives rise to the possibility of central adaption or habituation with repeated stimulation. Another possibility is a decrease in the myogenic contribution as the subject relaxes. This present study was not designed to investigate these phenomena, and further research in this area is needed.

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Ann Otol Rhinol Laryngol 97:1988

HEARING IMPAIRMENT IN RELATION TO VISCOELASTICITY OF MIDDLE EAR EFFUSIONS IN CHILDREN

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Both dynamic viscosity (η') and elasticity (G') of middle ear effusion were measured with an oscillating sphere magnetic rheometer and compared with the degree of conductive hearing loss in 65 ears of 40 children. There was a significant correlation between η' and the magnitude of the air-bone gap at 500 and 1,000 Hz, but there was no significant correlation between η' and the magnitude of the air-bone gap at 2,000 or 4,000 Hz. No significant correlation was noted between G' and the magnitude of the air-bone gap at 500, 1,000, 2,000, or 4,000 Hz. These results indicate that the η' of middle ear effusion has an effect on the amount of hearing impairment at frequencies below 1,000 Hz.

KEY WORDS — elasticity, hearing loss, middle ear effusion, otitis media with effusion, viscosity.

INTRODUCTION

The principal symptom of otitis media with effusion (OME) is conductive hearing loss due to the accumulation of serous or mucoid effusion in the middle ear. Middle ear effusion (MEE) has the viscoelastic properties common to tracheal and cervical mucus,[1] and also has a remarkable range of dynamic viscosity (η') and elasticity (G').[2] Studies of the relationship between the viscoelastic properties of MEE and the amount of hearing loss have never been described in humans, because of the difficulty in measuring viscoelasticity and the small amount of effusion available for analysis. In this study, both the η' and the G' of MEEs from children were determined using an oscillating sphere magnetic rheometer[3] and then were compared with the degree of conductive hearing loss in individual ears.

MATERIALS AND METHODS

Subjects. The children with OME were diagnosed by otoscopy using a pneumatic otoscope, pure tone audiometry, and measurements of middle ear impedance and tympanometric patterns. Forty children, 26 boys and 14 girls, participated in the study. So that the children would be reliable in responding to pure tone audiometry, we selected a mean age of 7.5 ± 1.6 years, with an age range of 6 to 13 years. Air and bone conduction audiometry were carried out in a soundproof chamber, using a Rion AA-61BN audiometer calibrated to the 1975 standards of the International Standards Organization. Immediately following audiometry, MEEs were collected from 65 ears of 40 children using the Juhn Tym-Tap at myringotomy, Each collected MEE was placed in a small plastic container, and the open end of the container was sealed with a cap to minimize evaporation. Each sample was stored at 4°C and measured for viscoelasticity within 24 hours.

Measurement of Viscoelasticity. Rheologic measurements were made with the oscillating sphere magnetic rheometer.[3] A block diagram of the rheometer is shown in Fig 1. Approximately 4 μL of the test sample with a small iron sphere with a radius of 100 μm was put into the sample cell and set in the space between the upper and lower magnetic poles. The iron sphere was oscillated in a vertical direction by application of a sinusoidally varying magnetic field gradient. The motion of the iron sphere was followed through a light microscope and transduced to an electric signal with an optoelectric tracer.

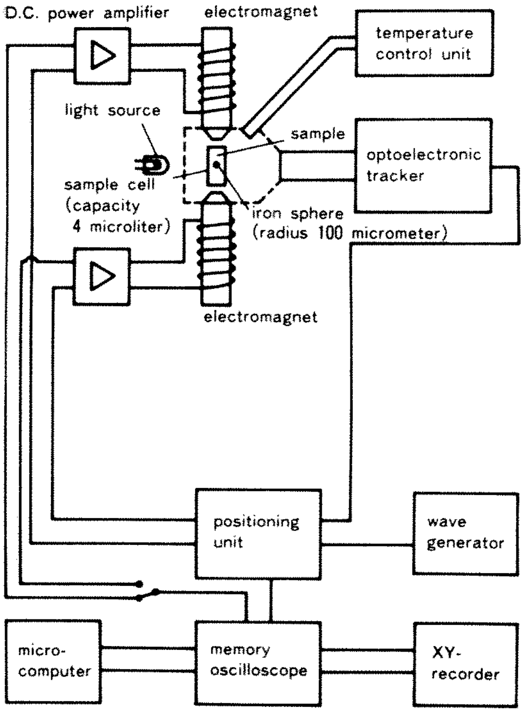

Fig 1. Diagram of oscillating sphere magnetic rheometer. (Reprinted from Majima et al.[2])

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Dynamic viscoelasticity was calculated according to the following formulas, using the determined values of the amplitude of the displacement of the iron sphere (X0 cm) and the phase lag of the sphere (δ rad) with respect to the oscillatory driving force (F0 dyne):

$$\text{elastic modulus } (G') = \frac{F0}{6\pi r X0} \cos\delta + \frac{2}{9}\rho_s r^2 \omega^2$$

$$\text{loss modulus } (G'') = \frac{F0}{6\pi r X0} \sin\delta$$

$$\text{dynamic viscosity } (\eta') = \frac{G''}{\omega}$$

where r is the radius (cm) of the iron sphere, ρ_s is the density of the sphere (g/cm³), and ω is the angular frequency (rad/s). The G′ is indicative of elastic behavior, and η′ is a measure of viscous behavior. Both G′ and η′ were determined simultaneously at 25°C at a frequency of 1 Hz.

Statistical Analysis. The correlation between the amount of hearing impairment and the viscoelasticity of MEE was determined by Spearman's rank correlation coefficient (one-sided analysis). Analysis of the correlation was performed from 10 to 40 dB in the magnitudes of the air-bone gap. The G′ and η′ values were subjected to common logarithmic conversion. Values reported are mean ± SD.

RESULTS

Viscoelasticity of MEE. In macroscopic appearance, eight effusions were serous, 13 were seropurulent, 16 were mucous, and 28 were mucopurulent. The G′ at 1 Hz in 65 freshly collected effusions ranged from 3.2 to 5,776 dyne/cm², and the mean value was 75.9 dyne/cm² with an SD of 0.99 log units. The η′ at 1 Hz in these effusions ranged from 0.1 to 5,990 poise, and the mean value was 8.0 poise with an SD of 1.01 log units.

Air-Bone Gap and Viscoelasticity of MEE. The mean magnitude of the audiometric air-bone gap at 500, 1,000, 2,000, and 4,000 Hz in 65 ears was 19.2, 25.1, 21.7, and 24.4 dB, respectively.

As shown in Fig 2, η′ of MEE was plotted against the magnitude of the air-bone gap at the evaluated frequency of incident sound. A significant correlation was observed between the η′ values of MEE and the magnitude of the air-bone gap at 500 Hz ($p < .05$; Fig 2). A significant correlation also was observed between these two parameters at 1,000 Hz ($p < .025$), but not observed at 2,000 or 4,000 Hz.

The correlation between the G′ values of MEE and the magnitude of the air-bone gap at 500, 1,000, 2,000, and 4,000 Hz was not significant. The results are summarized in the Table.

DISCUSSION

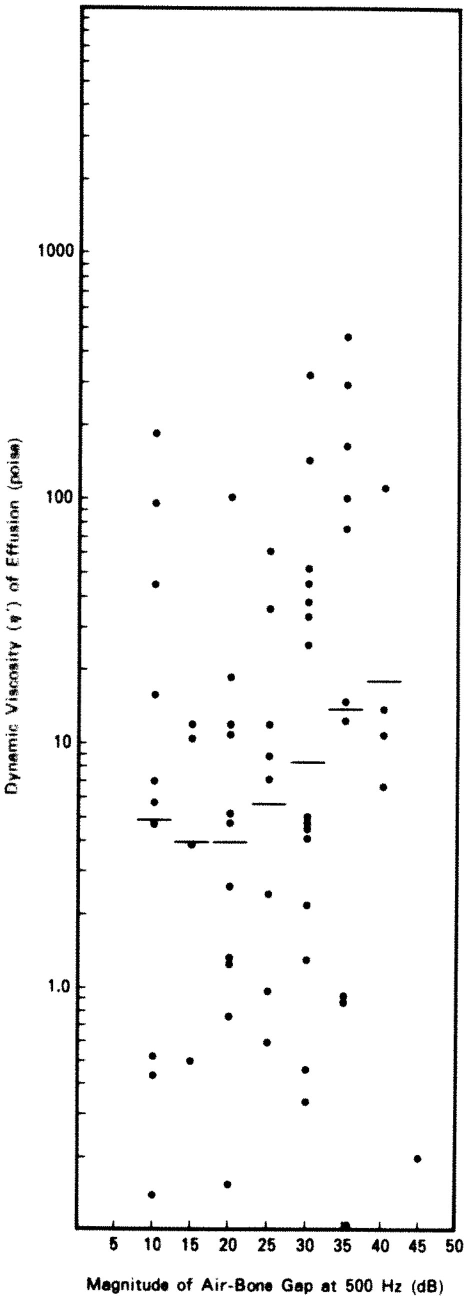

Fig 2. Dynamic viscosity (η′) of middle ear effusion versus magnitude of air-bone gap at 500 Hz. Correlation is significant ($r_s = 0.26014$, $n = 61$, $p < .05$). Dashes represent mean values of η′.

As MEE has viscoelastic properties in which η′ and G′ coexist, it is not easy for us to measure them separately. This is one of the main factors preventing advances in the accurate assessment of the rheologic properties of MEE. One of the ideal methods for determining the rheologic properties of MEE is the measure of dynamic viscoelasticity used in this study.[4] In this method, MEE is subjected to cyclic deformation, and the deformation response of the MEE is observed. Since this method provides fundamental viscoelasticity that can be correlated with in vivo conditions and molecular structures,[4] the measure of dynamic viscoelasticity is important for the assessment of the rheologic properties of MEE in

CORRELATION BETWEEN VISCOELASTIC PROPERTIES OF MEE AND MAGNITUDE OF AIR-BONE GAP

	Magnitude of Air-Bone Gap at Frequency of Incident Sound			
Viscoelasticity of MEE	*500 Hz*	*1,000 Hz*	*2,000 Hz*	*4,000 Hz*
Dynamic viscosity at 1 Hz	$p<.05$	$p<.025$	NS	NS
Elastic modulus at 1 Hz	NS	NS	NS	NS

MEE — middle ear effusion, NS — no significant correlation.

relation to the in vivo data, such as the amount of hearing loss. The oscillating sphere magnetic rheometer used in this study can measure the dynamic viscoelasticity in very small samples. In this rheometer, both G' and η' are determined simultaneously in a short time, and preliminary tests have established that rheologic changes of MEE during the measurement are negligible.

Although it appears that highly viscoelastic MEE would reduce the mobility of the tympanic membrane and ossicles much more than would slightly viscoelastic MEE, conflicting results have been reported. Goodhill and Holcomb[5] placed silicone oils of widely ranging viscosity into the middle ears of cats and found that there was a significant drop in response, by both air conduction and bone conduction, with increased viscosity. On the other hand, Bluestone et al[6] reported in patient material that the magnitude of the average (500, 1,000, and 2,000 Hz) air-bone gap was unrelated to the viscosity of MEE. Wiederhold et al[7] showed that there was no apparent relationship between the amount of hearing loss and the slope viscosity of the effusion obtained by ligation of the eustachian tube in cats. Brown et al[8] demonstrated in guinea pigs that a considerable viscosity difference between two different dextran solutions did not produce a corresponding change in hearing loss at 500, 1,000, 2,000, and 4,000 Hz. Marsh et al[9] showed in guinea pigs that the hearing loss induced by mucus did not differ significantly from that induced by saline. Thus, many studies have failed to find a relation between the viscosity and the severity of hearing loss.

Because the magnitude of the air-bone gap generally reflects the conductive component of impairments in hearing,[6] the present study is the first report concerning the relationship between the viscoelastic properties of MEE and the degree of hearing impairment in human subjects. A significant correlation was noted between η' and the magnitude of the air-bone gap at 500 and 1,000 Hz. The correlation between G' and the magnitude of the air-bone gap was not significant. These results indicate that the rheologic properties, especially the η', of effusion do have an effect on the amount of hearing impairment at frequencies at and below 1,000 Hz in children with OME. As shown in Fig 2, however, the η' at any given magnitude of the air-bone gap varies widely. For example, MEE had a remarkable range of η', from 0.3 to 328 poise, when the magnitude of the air-bone gap was 30 dB. This fact suggests that the rheologic properties of MEE are not the most important determinants of the amount of hearing loss. Other factors, such as volume of effusion in the middle ear,[7] might contribute much to the degree of conductive impairment.

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Ann Otol Rhinol Laryngol 97:1988

DYSPHONIA CAUSED BY FORESTIER'S DISEASE

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A case of diffuse idiopathic skeletal hyperostosis (Forestier's disease) causing dysphonia as the presenting and only symptom is reported. The dysphonia is attributed to the mass effect in the hypopharynx and the mild pressure on the larynx. The bony mass anterior to the vertebral body is demonstrated by CT scan for the first time in the literature on Forestier's disease.

KEY WORDS — diffuse idiopathic skeletal hyperostosis, dysphonia, Forestier's disease.

In 1950, Forestier and Rotes-Querol[1] described patients with abnormal ossification involving the anterior and lateral aspects of the vertebral column. They differed from patients with ankylosing spondylitis in the absence of lesions of the apophyseal and sacroiliac joints, and from patients with degenerative spondylosis in the absence of narrowing of the intervertebral disc space. Forestier and Rotes-Querol believed that this disease was not significant clinically, except for some stiffness of the spine; however, patients with Forestier's disease, in addition to incapacitating back pain, may suffer occasionally from dysphagia, dysphonia, and even spinal cord compression.[2-7] Although Forestier's disease is not uncommon, it is mentioned rarely in the otolaryngologic literature,[3,5] and not at all in the major otolaryngologic textbooks.

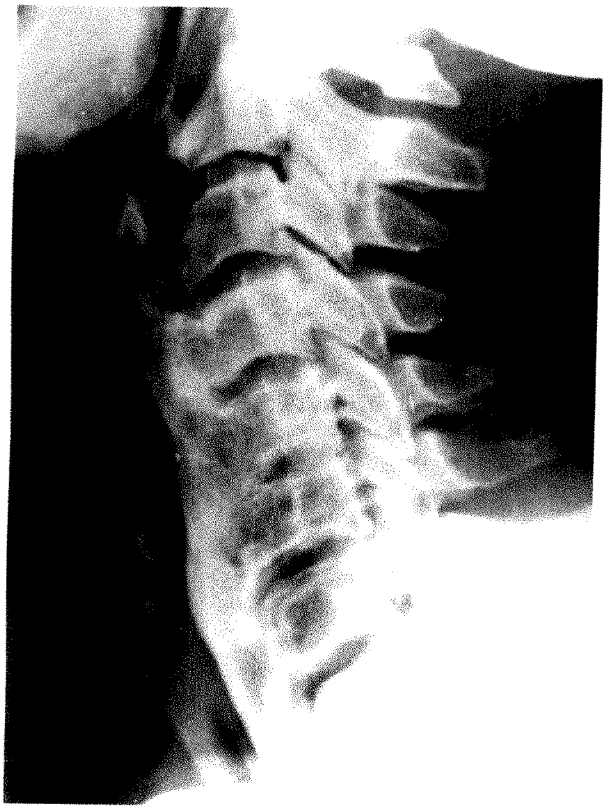

Fig 1. Lateral cervical spine radiograph showing extensive ossification along anterior border of vertebral bodies.

CASE REPORT

A 61-year-old man complained of gradual voice changes, described by him as hoarseness. There was neither cervical pain nor difficulty in swallowing.

Results of a general physical examination were negative. The ears, nose, and throat were normal in appearance. The patient had no true hoarseness, but his voice was muffled as in "hot potato voice." Indirect laryngoscopy revealed a bulging of the posterior hypopharyngeal wall that partly obscured the laryngeal inlet. The larynx was visualized with difficulty, and no abnormality in the larynx proper was found.

A lateral cervical radiograph revealed a large abnormal bony mass due to extensive ossification along the anterior and lateral aspects of the cervical vertebral bodies (Fig 1). A computed tomographic scan of the neck (Fig 2) showed the bony mass bulg-

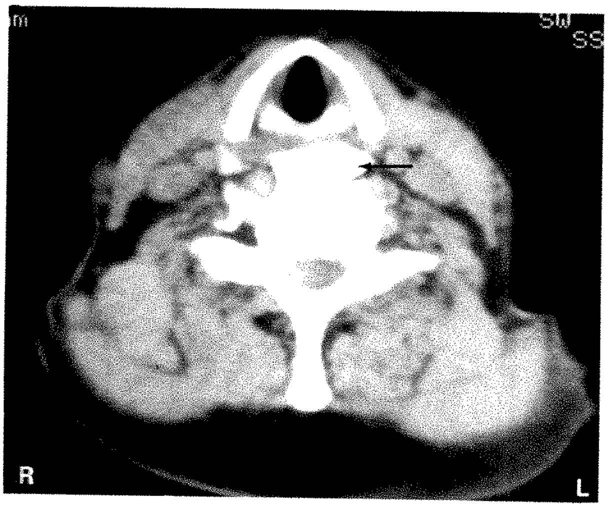

Fig 2. Computed tomographic scan of neck at level of vocal cords showing abnormal bony mass (arrow) attached to anterior aspect of vertebral body, slightly compressing posterior aspect of larynx.

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ing at the anterior border of the vertebral bodies, with some compression on the posterior aspect of the larynx. The thoracic and lumbar spine was found to be normal. The patient was reassured regarding the nature of his condition, and no treatment was suggested.

DISCUSSION

Dysphagia and laryngeal symptoms such as dysphonia, hoarseness, cough, aspiration, and a lump in the throat in patients suffering from cervical spinal diseases are well documented in the literature.[2-7] In an advanced case, one may see at laryngoscopy a mass protruding into the hypopharynx, which may preclude a clear view of the larynx. The laryngeal symptoms presumably are due to the pressure on the larynx from behind by the bony bulging or are due to edema of the vocal cords, although paralysis of the recurrent laryngeal nerves has been noted in certain instances.[3]

Only rarely, the association between diffuse idiopathic skeletal hyperostosis (Forestier's disease) and dysphonia is reported.[4,6] The present case is unique in that dysphonia was the only clinical symptom and no dysphagia or cervical stiffness were noted. The dysphonia is attributed to the mass effect in the hypopharynx and the mild pressure on the larynx, which for the first time in the literature on Forestier's disease is demonstrated by CT scan.

This condition is a disease of unknown pathogenesis that affects the older age group. The ossification usually involves the anterior spinal ligament linearly, most commonly in the thoracic and lumbar regions. Some patients show a variety of extraspinal hyperostotic manifestations.[8] In symptomatic patients, surgical excision of the bony mass results in a satisfactory outcome.[4]

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XXI CONGRESS OF THE INTERNATIONAL ASSOCIATION OF LOGOPEDICS AND PHONIATRICS

The XXI Congress of the International Association of Logopedics and Phoniatrics will be held Aug 6-10, 1989, in Prague. For further information, contact the Secretariat, XXI Congress of the International Association of Logopedics and Phoniatrics, Czechoslovak Medical Society J. E. Purkyne, 120 26 Prague 2, Vitezneho unora 31, Czechoslovakia; telephone 29 41 41-4, telex 121 293.

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RELATIONSHIP OF EUSTACHIAN TUBE BONY LANDMARKS AND TEMPORAL BONE PNEUMATIZATION

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Anatomic and functional differences of the eustachian tube have been suggested as etiologic factors in patients with otitis media. We studied eustachian tube lengths and vectors of the tensor veli palatini muscle in 25 unilateral specimens from adult human cadavers. The extent of temporal bone pneumatization, as determined by computed tomography and plain lateral radiographs, was used as an indicator of prior otitis media. Increased length of the cartilaginous eustachian tube was associated positively ($r = .53$, $p < .01$) with volume of pneumatization. However, neither the length of the bony eustachian tube nor the vector of maximum pull of the tensor veli palatini muscle was associated statistically with the extent of pneumatization. It may be that the longer cartilaginous eustachian tube is more protective of the middle ear.

KEY WORDS — eustachian tube, mastoid, otitis media, temporal bone.

INTRODUCTION

The eustachian tube generally is regarded as an etiologic factor in patients with otitis media. Anatomic[1,2] and functional[3,4] differences of the eustachian tube have been suggested. Additionally, patients with otitis media have been suggested to have differences of the skull base: Plester[5] found the angle (on lateral cephalometric radiograph) subtended by the posterior border of the hard palate, the clinoid, and the clivus to be narrower in adults with cholesteatoma than in adults with extended pneumatization of the temporal bones. Mann et al[6] report good tubal function to coincide with mesocephalic or brachycephalic patterns (on lateral cephalometric radiograph) and poor tubal function with dolicocephalic morphologic patterns. Doyle,[7] using ethnicity to identify those with otitis media, suggested that the vertical height of the pterygoid process is shorter. Thus, several studies report cranial differences in patients with otitis media.

The present study of unilateral adult cadaver specimens searched for associations between eustachian length and vector of the tensor tympani muscle and the extent of temporal bone pneumatization. As the tensor veli palatini is the only active opener of the eustachian lumen, special attention was focused on this muscle. Abundant documentation shows that ears with otitis media characteristically have small mastoid air cell systems[8,9]; the mechanism is compromised middle ear ventilation before skeletal maturation.[10,11]

MATERIALS AND METHODS

We obtained 30 formalin-fixed adult skull half specimens, cut midsagittally. All were from humans who antemortem had bequeathed their bodies to science; most were white, the remainder black. No specific racial, age, or gender information was available. Though none had died of ear disease, other information on their otologic histories was not available.[12] Five specimens could not be included because of inadvertent interim dissection. No right and left specimens were from the same cadaver; 15 right-sided and ten left-sided specimens were studied. Three of these specimens were not usable for all measurements: the pterygoid lip of one had been fractured postmortem, the pterygoid lip of another was tiny and ill-defined, and the bony eustachian tube of one had been sawed.

Runström II lateral radiographs, Law lateral radiographs, and computed tomography were used to describe the extent of temporal bone pneumatization; CT is the most accurate method.[12] For the lateral radiographs, the central x-ray beam was projected through the external ear canal. The source-to-target distance was 120 cm, so that linear magnification was less than x1.01; this magnification was considered negligible and was ignored in data computations. The outline of pneumatization on the radiographic image was traced onto paper. In contrast to Diamant's[8] method of excluding the antrum region on the tracings, this region was included. The mean of two planimetry measurements of each image was used; if the initial two measurements did not agree within 0.5 cm^2 of each other, then the mean of four measurements was used.

The CT images were obtained from 1.5-mm thick sections using a General Electric 8800-C scanner. The outline of pneumatization, including the middle ear, of each section was traced on the video display screen, and computer-determined areas were recorded. Pneumatization volume was calculated by multiplying the sum of the traced areas (in square centimeters) by 0.15 (the thickness in centimeters of the imaged slice).

With these unilateral specimens, a limited num-

From the Division of Otolaryngology, Emory University School of Medicine, Atlanta. Supported by Georgia Lions Lighthouse.

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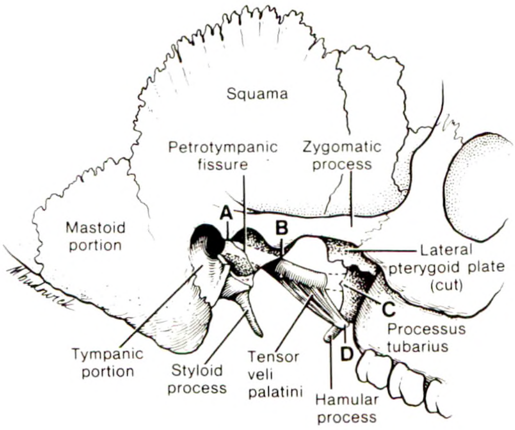

Fig 1. Diagram of bony landmarks (A,B,C,D) studied, for right-sided specimen as viewed anterolaterally. Landmarks (points) are not necessarily in same plane.

ber of skull base measurements pertinent to the eustachian tube were available. Four landmarks (points) were chosen (Fig 1):

A: the bony annulus of the tympanic membrane at the petrotympanic fissure.
B: the anteromedial extent of the osseous tube, or the anteromedial extent of the "isthmus" as defined by Sadé et al.[13] This landmark was determined by needle palpation from the inferior perspective; the easily palpable spine of the sphenoid, located just lateral to this landmark, offered guidance for the needle palpation.
C: the apex of the lip of the pterygoid process. Also known as the processus tubarius, the lip is situated on the posterior border of the medial plate of the pterygoid process. The lip represents the anteromedial attachment of the cartilaginous eustachian tube.
D: the groove in which the tendon of the tensor veli palatini muscle curves anterolaterally around the hamular process.

The linear measurements were done with calipers to the nearest half millimeter. Six direct linear measurements were made between landmarks:

AB: the length of the bony eustachian tube. This weakly approximates Doyle's[7] "variable 5." The luminal length may, of course, be longer.
BC: the length of the cartilaginous eustachian tube. This approximates Doyle's "variable 8." The luminal length is probably longer.
AC: the total eustachian length.
CD: the minimum length of the tensor veli palatini vector as it relates to the tube. This approximates Doyle's "variable 11."
BD: the maximum length of the tensor veli palatini vector as it relates to the eustachian tube. This approximates Doyle's "variable 9."
AD: Doyle did not measure this distance. However, it may confirm measurements AB and BD, and of the bony landmarks used in this study, A and D can best be approximated at CT.

The angle subtended by CBD was computed from the formula for determining an angle of an obtuse triangle.[14] This angle approximates Doyle's "variable 21." The angle's sine function, which approximates Doyle's "variable 22," depicts the component vector of the tensor veli palatini muscle that serves to open the tube within the BCD plane.

Each measurement for each specimen was carried out independently. The mean of two determinations of each length was used for computation; excellent precision of measurements was apparent. The data of the left-sided and right-sided specimens were analyzed separately, with nearly identical findings; the grouped data are presented. For statistical assessment of a relationship between numeric

MEASUREMENTS OF THIS STUDY AS COMPARED TO WORK OF OTHERS

		Present Study		*Doyle*[7]	*Graves and Edwards*[15]	*Konstantinov and Senyukov*[16]	
		Left	*Right*	*Left**	—	*Left*	*Right*
No. of specimens		10†	15§	160	—	40	40
Length of bony tube	Mean	14.6 mm	16.3 mm	11.7 mm	—	10 mm	9 mm
(measurement AB)	Range	11.5-18.0	12.0-22.0	—	11-12 mm	—	—
Length of cartilaginous tube	Mean	22.8 mm	22.3 mm	28.0 mm	—	28 mm	28 mm
(measurement BC)	Range	19.5-30.0	14.7-27.7	—	24-25 mm	—	—
Total tube length	Mean	37.8 mm	38.9 mm	—	—	38 mm	37 mm
(measurement AC)	Range	33.7-42.2	31.5-45.0	—	31-38 mm	—	—
Lip to hamulus	Mean	16.7 mm	17.7 mm	16.9 mm	—	—	—
(measurement CD)	Range	12.8-21.2	12.2-22.5	—	—	—	—
Isthmus to hamulus	Mean	35.2 mm	35.5 mm	39.4 mm	—	—	—
(measurement BD)	Range	29.5-43.0	28.0-41.0	—	—	—	—
Annulus to hamulus	Mean	49.9 mm	51.8 mm	—	—	—	—
(measurement AD)	Range	42.2-57.0	44.0-59.8	—	—	—	—

Dashes indicate data not specified.

*Black and white, male and female specimens in equal numbers; right-sided specimens not studied.

†Only nine specimens were usable for measurements AC, BC, and CD.

§Only 13 specimens were usable for AC; 14 for BC and CD; and 14 for AB, AC, and AD.

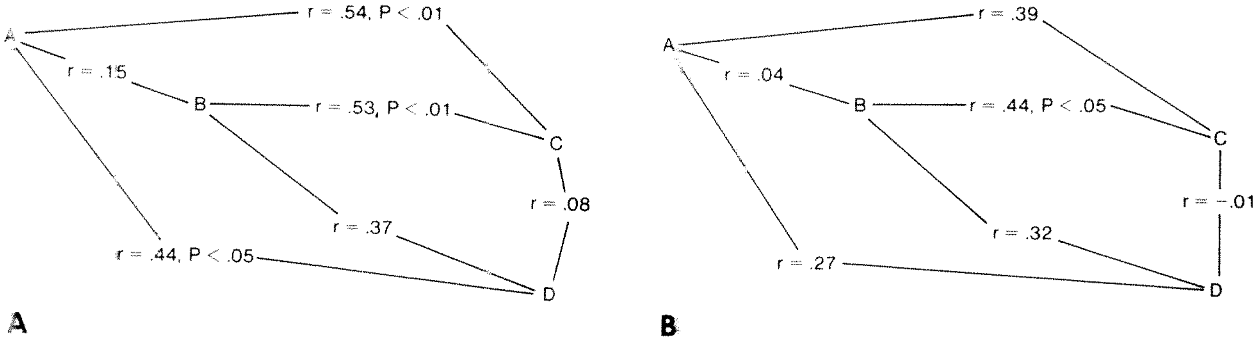

Fig 2. Relationships of measurements between bony landmarks of eustachian tube and A) volume of temporal bone pneumatization measured by computed tomography and B) area of temporal bone pneumatization measured on Law lateral radiograph. Right-sided and left-sided specimen data are combined.

variables, we used the Pearson product moment correlation (r). For r values sufficient to reject the null hypothesis (of no association), the p value ($p < .05$ or $p < .01$) is stated. Student's *t* test of independent means was used in comparing the pneumatization of these specimens with "normal."

RESULTS

The lengths of the bony and cartilaginous eustachian tube were nearly identical for the left-sided and right-sided specimens and acceptably concurred with lengths reported by others[7,15,16]; the discrepancies are probably attributable to varying designations of the bony-cartilaginous junction. The other measurements, including size of pneumatization, exhibited nearly identical right-sided and left-sided findings (see Table[7,15,16]). Temporal bone pneumatization, as assessed by the Runström II radiograph, was quite similar to "normal": Diamant's[8] normal population (56 ears of 28 persons) had a 10.78-cm^2 mean, a range of 0 to 27.6, and a standard deviation of 4.8. The 25 specimens of this study had a 10.39-cm^2 mean, a range of 1.5 to 21.5, and a standard deviation of 5. (With correction for magnification, and ignoring Diamant's exclusion of the antrum in tracing the outline of pneumatization, $t = .101$; 79 df, $p > .9$.)

Increased length of the cartilaginous tube correlated positively ($r = .53$, $p < .01$) with the volume of temporal bone pneumatization (Fig 2A). Similar findings resulted when pneumatization was assessed by the Law lateral radiographs: $r = .44$, $p < .05$ (Fig 2B). A similar trend was suggested when pneumatization was assessed by the classic but less accurate Runström II radiograph. That the Law results correlated better than the Runström II is expected: pneumatization assessed by the Law radiograph has a better fit with CT-determined pneumatization than does the Runström II.[12] Figure 2 shows that AB and BC are confirmed by the AC correlation, and that AB and BD are confirmed by AD.

The size of the processus tubarius did not correlate with the volume of pneumatization. The angle subtended by CBD was quite variable among the 23 usable specimens: 12° to 32°. Regarding the angle's sine, which is seemingly the best expression of the component vector of the tensor veli palatini muscle, a trend with pneumatization volume may be suggested: $r = .27$.

DISCUSSION

The inferences made from this study may be limited by two aspects of the specimens. First, perhaps the findings would be otherwise if the otitis media status of each specimen had been defined differently. Would specimens ranked by severity of clinical otitis, from persons prospectively studied over a lifetime, be rated as were the specimens of this study? Second is the problem of the unilateral study of an essentially bilateral disease. Would the inferences be substantiated if the mean of the right and left ears' pneumatization size were used as the indicator of the otitis media condition? Is there bilateral symmetry of the bony landmarks of the eustachian tubes?

The three-dimensional nature of the eustachian apparatus has not been addressed by this study. We offer no data regarding the angle of juncture of the cartilaginous portion with the bony portion of the eustachian tube.

These adult human specimens exhibited a significant relationship between the length of the cartilaginous eustachian tube and the extent of temporal bone pneumatization. The finding that the vector of maximum pull for opening the tube did not relate statistically to pneumatization size is of undetermined import. The important message is the relationship of eustachian tube (cranial base) differences with an indicator of the otitis media condition. A causal relationship, with the longer cartilaginous tube perhaps being more protective of the middle ear, can be inferred.

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UNIVERSITY OF CAPE TOWN, POSTGRADUATE MEDICAL CENTRE

The South African Society of Otolaryngology Course in Otology will be held October 16-20, 1988. The Head and Neck Oncology Society of South Africa will hold the 3rd National Congress on October 21, 1988. Both meetings will be held at the Mount Nelson Hotel, Cape Town, South Africa. For further information, contact Deborah McTeer, Postgraduate Medical Centre, University of Cape Town Medical School, Observatory, 7925, Cape, South Africa; Telephone 471250 ext 348.

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REVERSIBLE CONDUCTIVE HEARING LOSS IN MICE

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Fibrin tissue adhesive was injected into the right ears of four 7-week-old CBA/J mice. Auditory brain stem responses (ABRs) were used to monitor changes in auditory sensitivity over the next 26 days, after which the middle ears and cochleas were examined histologically. Mean maximum ABR threshold shifts were as great as 36 dB, and were larger for higher frequencies than for lower. Maximum shifts occurred between 1 and 8 days; by 26 days, thresholds had returned to intensity levels observed before injection.

KEY WORDS — auditory brain stem response, conductive hearing loss, fibrin sealant.

INTRODUCTION

In this study we examined the effects of injecting a fibrin tissue adhesive into the middle ears of four CBA/J mice. Previous studies from this laboratory have shown that conductive hearing loss during critical developmental periods causes changes in central auditory structures.[1-3] We reasoned that fibrin tissue adhesive, which acts like connective tissue, could create conductive hearing losses that would reverse themselves as the material eventually was resorbed. We wished to know the extent of the conductive hearing loss thus created, its distribution across frequencies in the low and middle frequency range of hearing, the time course of the loss, and the effects of the adhesive on middle ear structures.

Fibrin Sealant. The fibrin tissue adhesive used in this study (Fibrin Sealant, Immuno Corp, Vienna) is composed of a solution of fibrinogen, thrombin, and Factor XIII (a fibrin-stabilizing factor). When mixed together, these substances have strong adhesive properties and set into a rubberlike mass within 2 hours.[4]

This tissue adhesive has been used in Europe in various operations on humans,[5] including otolaryngologic procedures.[4] In the United States, it has been used in experimental ossicular operations on chinchillas.[6]

MATERIALS AND METHODS

Two male and two female CBA/J mice, all from the same litter, were used in this study. At 49 days of age, they were sedated and their left cochleas were removed in order to prevent crossover of auditory stimuli at high sound pressure levels (SPLs).

The first of seven auditory brain stem response (ABR) latency-intensity functions for each mouse was obtained on day 50. For this and all subsequent recording sessions the following procedure was used.

The mice were sedated with chloral hydrate in a normal saline solution (380 mg/kg, intraperitoneally) and placed on a heating pad. Temperature was monitored rectally during each session, which lasted approximately 1 hour.

The test stimuli were tone bursts at 4, 8, and 16 kHz that had linear envelopes with 0.5-ms rise/fall times and a 0.5-ms plateau. Stimuli were generated by a Nicolet Pathfinder II SM700 multisignal auditory generator at a rate of 27.7 stimuli/s and transduced through an Etymotic Research ER-2 wide frequency range insert earphone[7] placed in a speculum in the right ear canal. Two-channel ABR recordings were obtained with subcutaneous 30-gauge stainless steel electrodes placed at the vertex and over the right and left bullae, with the ground electrode near the base of the tail. The physiologic response was filtered through a 100- to 3 000-Hz bandwidth with a 12-dB/octave slope and amplified with a full-scale input sensitivity of 20 μV peak-to-peak. Averages of 512 sweeps across a 10-ms time window were obtained for each test condition.

Stimuli were presented at several SPLs for each frequency, with starting levels of 110 dB peak SPL for 4 kHz, and 100 dB peak SPL for 8 and 16 kHz. Intensity was decreased in 10-dB steps as threshold was approached, and in 20-dB steps at higher intensities.

In the initial ABR recordings on day 50, baseline latency-intensity functions were obtained for intensities between 60 and 110 dB peak SPL at 4 kHz, and between 40 and 100 dB peak SPL at 8 and 16 kHz.

On day 51, the mice were sedated again with chloral hydrate and approximately 0.02 mL of the fibrin solution was injected through the posterior inferior quadrant of the right tympanic membrane. Additional ABRs were recorded from each mouse at

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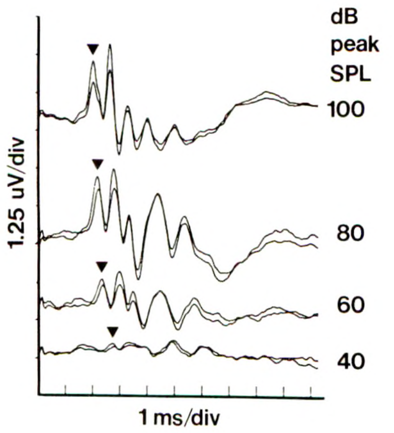

Fig 1. Auditory brain stem responses obtained from normal 7-week-old CBA/J mouse. Stimuli were 8-kHz tone bursts at intensity levels ranging from 100 dB peak SPL (top tracing) to 40 dB peak SPL (bottom tracing). Inverted triangles identify wave I.

1, 4, 8, 11, 15, and 26 days after the fibrin injection.

To determine the degree of variability to be expected from reinsertion of the speculum and earphone during repeated tests on the same animals, we previously had done a series of recordings across several days on a single (normal) mouse using these same stimulus and recording arrangements. The maximum latency variability was 0.02 ms for each of the three frequencies analyzed.

Two days after the final ABRs were obtained, the mice were given an overdose of anesthesia and transcardially perfused with Tyrode's solution containing 1% sodium nitrite followed by mixed aldehydes (3% glutaraldehyde, 1.5% paraformaldehyde, in 0.1 *M* cacodylate buffer, pH 7.2). The right and left periotic bones were removed and postfixed for 24 hours at 4°C in the same mixed aldehyde solution. Then they were decalcified in 8% EDTA for 10 days, dehydrated in an ethanol series, and embedded in glycol methacrylate. Four-micron serial sections were cut in the plane of the modiolus; every tenth section was stained with 0.1% toluidine blue for examination by light microscopy.

RESULTS

Auditory Brain Stem Response. A typical ABR latency-intensity function for an 8-kHz tone burst obtained from a normal mouse is shown in Fig 1. Wave I, identified by an inverted triangle, was selected for analysis because it was clearly visible in all recordings and is less affected by temperature shifts than later components of the ABR. Wave I typically occurred at approximately 2.05 ms after the stimulus for 4-kHz tone bursts (110 dB peak SPL), at 1.95 ms for 8-kHz tone bursts (100 dB peak SPL), and at 1.85 ms for 16-kHz tone bursts (100 dB peak SPL). Because the insert earphone has an acoustic delay line of 0.9 ms, the actual latency of wave I in Fig 1 would be about 1.0 ms. As the intensity of the stimulus was decreased, there was a predictable increase in latency and decrease in amplitude of all waves, with wave I latency increasing by about 0.6 ms at the lowest intensities.

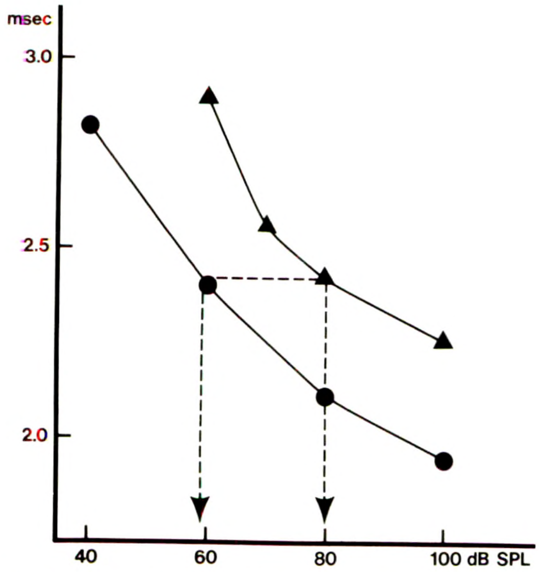

Fig 2. Method used to determine differences between auditory brain stem response latency-intensity functions before (●) and after (▼) injection of fibrin. At least three points were compared for each condition. This example shows derivation of decibel shift at one of three points.

Latency-intensity functions for wave I were plotted at each of the three test frequencies for the session before injection, and for each of the six sessions after injection. The shift (in decibels) of the latency-intensity function was derived by subtracting the intensity value corresponding to a given ABR latency before injection from the intensity value obtained at each of the six sessions after injection. An example of this process is shown in Fig 2, where the lower latency-intensity function was obtained before injection while the upper function was obtained during one of the tests after injection. Com-

TABLE 1. SHIFTS IN AUDITORY BRAIN STEM RESPONSE LATENCY-INTENSITY FUNCTIONS

Days After Injection		*4 kHz*	*8 kHz*	*16 kHz*
1	Mean	27.7	31.5	26.0
	SD	6.1	6.9	7.1
4	Mean	20.6	29.8	35.6
	SD	5.8	8.4	7.8
8	Mean	8.1	14.6	22.7
	SD	6.8	9.6	12.5
11	Mean	6.5	12.3	11.9
	SD	6.8	7.9	8.7
15	Mean	5.8	12.3	8.5
	SD	7.4	7.9	9.6
26	Mean	− 3.5	− 0.2	− 2.5
	SD	5.5	7.3	6.7

Shows mean shift and one standard deviation (SD), in decibels, of auditory brain stem response latency-intensity functions from functions obtained before injection for four mice at three intensities at 4, 8, and 16 kHz on basis of day after injection.

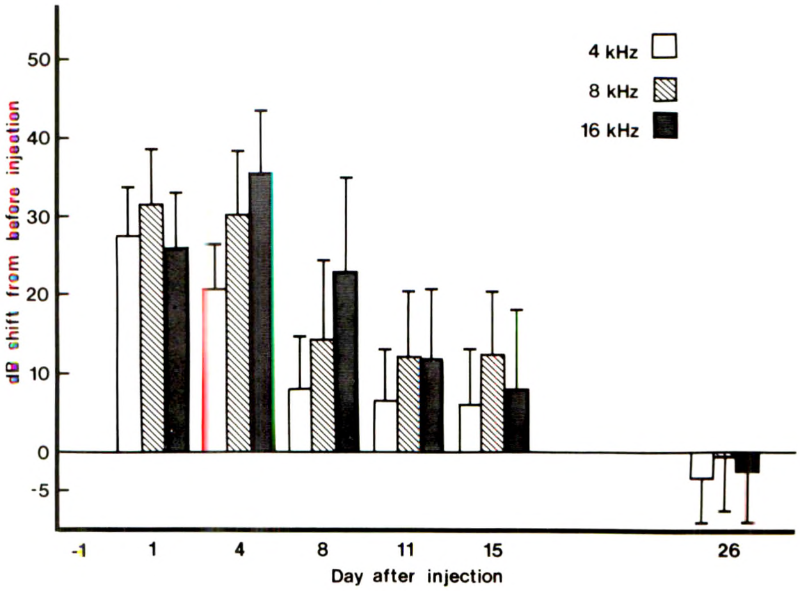

Fig 3. Shift, in decibels, of auditory brain stem response latency-intensity functions on basis of frequency and days after injection of fibrin. Bars indicate one standard deviation.

parison of intensity levels necessary to obtain similar latencies shows a shift of 21 dB (from 59 to 80 dB) in this example. The decibel shifts after injection reported in this paper represent an average of three corresponding points on each latency-intensity function (Fig 2).

The latency-intensity shifts in the ABRs as a function of frequency and days after injection are summarized in Table 1 and graphed in Fig 3. The bars represent the mean shifts of the latency-intensity functions and show one standard deviation. The largest latency shift occurred during the first 4 to 8 days after injection, with greater overall shifts at 8 and 16 kHz than at 4 kHz. Three of the animals showed recovery back to baseline by 15 days; the fourth returned to baseline by 26 days.

A three-way analysis of variance (frequency by day by intensity) with repeated measures indicated significant effects for frequency and day, and a frequency-by-day interaction of these variables (Table 2). Range testing using the Newman-Keuls statistic revealed the frequency effect to be due to smaller shifts at 4 kHz than at 8 or 16 kHz ($p < .05$). Statistical comparison of shifts as a function of the time after injection indicated that all shifts except those on the 26th day were significantly different from the recordings before injection ($p < .01$). The significant interaction of frequency and days is seen in the occurrence of maximum decibel shifts for different frequencies on different days (4 and 8 kHz on day 1; 16 kHz on day 4) and nonparallel recovery rates across frequencies.

Statistical analyses also were completed on the ABR wave I absolute latency data. Results were consistent with the decibel shift data with the predictable addition of a significant main effect for intensity.

The right tympanic membrane was viewed mi-

TABLE 2. RESULTS OF ANALYSIS OF VARIANCE FOR SHIFT OF AUDITORY BRAIN STEM RESPONSE LATENCY-INTENSITY FUNCTION FROM FUNCTION OBTAINED BEFORE INJECTION

Source of Variation	*Degrees of Freedom*	*Sums of Squares*	*Mean Squares*	*F Ratio*	*Probability Level*
Frequency	2	1,736.33	868.17	7.19	0.02*
Error	6	724.78	120.80		
Intensity	2	35.47	17.74	0.25	0.79
Error	6	424.94	70.82		
Days	5	25,878.89	5,175.77	34.59	0.00001†
Error	15	2,244.37	149.62		
Frequency x intensity	4	169.74	42.43	1.56	0.25
Error	12	326.78	27.23		
Frequency x days	10	1,678.66	167.87	8.20	0.00002†
Error	30	614.39	20.48		
Intensity x days	10	447.23	44.72	1.50	0.19
Error	30	892.35	29.74		
Frequency x intensity x days	20	211.09	10.55	0.67	0.84
Error	60	946.54	15.77		
Total	215	41,615.23			

*Significant beyond 5% level.

†Significant beyond 1% level.

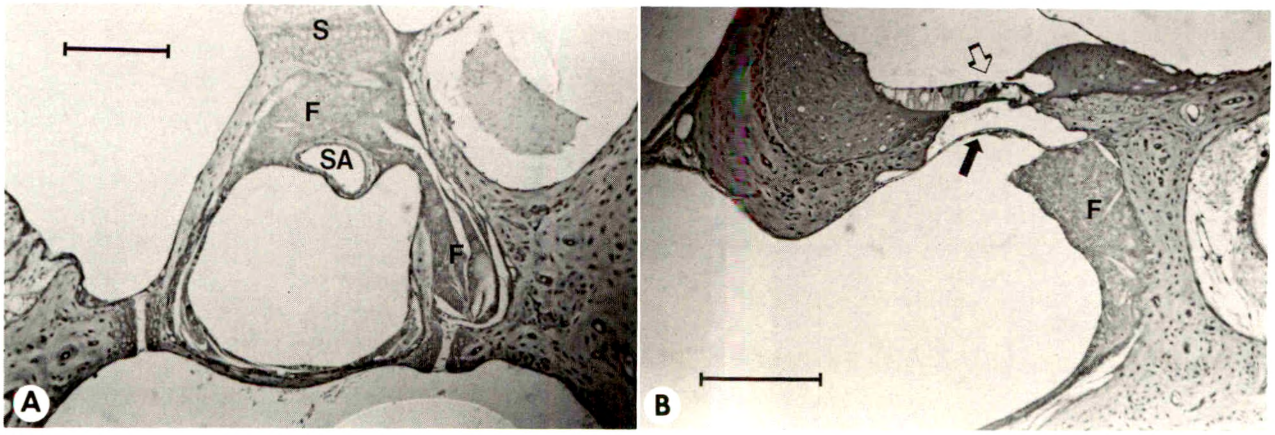

Fig 4. Light microscopy (toluidine blue stain; lines equal 150 μm, respectively). A) Section through stapes (S) showing residual fibrin sealant (F) between crura and around stapedial artery (SA). B) Section through round window membrane (closed arrow) and basal turn organ of Corti (open arrow) showing residual fibrin sealant in round window niche.

croscopically prior to each ABR procedure. The mouse that returned to baseline in 26 days rather than 15 had a fracture of the tip of the manubrium immediately following injection, which ultimately repaired. In all four mice, fibrin was seen behind the retracted tympanic membrane until 11 days after injection. In one animal, there was a perforation in the posterior inferior quadrant until the 15th day after injection. The tympanic membrane appeared normal at 26 days after injection in all four mice.

Histologic Findings. Light microscopic examination showed total or near-total destruction of the left organ of Corti; the right organ of Corti appeared normal in all four mice. In the middle ears, there were minimal or no abnormalities in the tympanic membrane, ossicles, and other middle ear tissues.

Little fibrin remained, and Fig 4 shows worst-case examples. In all four mice, there was some fibrin in the area of the crura or footplate of the stapes; for instance, in Fig 4A there is fibrin in the area of the posterior crus and the stapedial artery. Two ears had fibrin against the round window; one is pictured in Fig 4B. The other two ears had traces of fibrin at the round window niche, but these did not impinge upon the membrane. In addition, there was fibrin around the posterior ligament of the incus in one mouse.

DISCUSSION

This study demonstrates that fibrin injected into the middle ear space of CBA/J mice creates a conductive hearing loss that peaks at 4 days and lasts less than 26 days.

Previous investigators have used various methods to create temporary conductive losses. Silverman and Clopton[8] and Clopton and Silverman[9] ligated the external auditory meatus, which causes greater conductive losses at high than at low frequencies.[9] Kerr et al[10] injected ear impression compound into the external ears of chicks; comparison of stimulus levels required for evoked potential thresholds with and without the earplug indicated mean attenuation levels of 40.3 dB between 0.125 and 3 kHz, with decreasing attenuation at 4 and 5 kHz. In our laboratory, Webster and Webster[1-3] surgically removed the external auditory meatus.

While each of these methods successfully creates reversible conductive hearing losses in one or both ears, each also has an inherent problem due to the closing of the external auditory meatus, which causes accumulation of epithelial debris on the tympanic membrane. This accumulation is difficult to remove without damaging the membrane; thus, the membrane remains mass loaded and the conductive loss is not fully reversed. The debris accumulation also can cause tympanic membrane perforation and cholesteatomas. These problems do not occur when fibrin is injected into the middle ear space.

Another type of tissue adhesive also has been investigated, but with less success. Chen and Harner[11] placed butyl 2-cyanoacrylate (Histoacryl) tissue adhesive on the stapes footplate and round window in chinchillas. They observed reactions in the middle ear mucosa and air cells, inflammation of the inner ear, ossification, and loss of organ of Corti architecture. Moreover, this adhesive was not resorbed and therefore the conductive loss was not reversible.

The auditory brain stem response is used widely to draw inferences regarding hearing sensitivity in both research and clinical tests. In the present study, thresholds of responses prior to injection were obtained for tone bursts with total durations of 1.5 ms at average intensities of approximately 60 dB peak SPL at 4 kHz and 40 dB peak SPL at 8 and 16 kHz. The quantitative data of this study were derived from shifts in the ABR thresholds over a 26-day period after fibrin injection. It is of interest that the threshold data obtained in this ABR study compare favorably with previous literature on hearing sensitivity in mice[12-14] if stimulus and presentation differences are taken into account.

We recognize that our testing covers only the low and middle frequency regions of hearing in mice (4 to 16 kHz) and that mice hear well up to at least 64 kHz.[12-14] It is possible that the fibrin adhesive would have a residual effect at these higher frequencies, particularly since any trans-round window material would affect the basal turn and thus the high frequencies. We doubt this is the case, however, since our light microscopy revealed no morphologic abnormalities in any region of the cochlea.

The differential effects of the fibrin at various frequencies may be related to changes in the middle ear transmission system. Changes in mass, movement of the tympanic membrane and ossicles, and tissue and pressure in the middle ear space may have contributed individually or in combination to the observed changes. While mass loading of a system has a more pronounced effect on higher than on lower frequencies, the extent of a mass effect in this study in unknown, since the exact placement of the fibrin adhesive in relation to middle ear structures could not be determined.

The extent of the threshold shifts undoubtedly is related to the actual amount of fibrin injected into the middle ear and to the space(s) occupied by the substance. These factors would account for some of the variability among the four mice and for the differences in rates of recovery of the ABR to preinjection levels. The fact that ABR latency-intensity functions were obtained in 20- and 10-dB intensity steps precludes precise determination of the details of threshold changes; however, the data do show recovery to preinjection levels. Because this study was conducted over only about 4 weeks, we suspect that the residual fibrin observed during histologic examination would be resorbed given more time.

We do not advocate that these materials be used in humans. The fibrinogen and Factor XIII are derived as cryoprecipitates isolated from pooled human plasma and carry a risk of transmitting hepatitis and other infectious agents. Epstein et al[15] have used these same materials and have described a method of isolating the fibrinogen adhesive from an individual's plasma to reduce such risks. In our mouse material, there could have been an antigen insult to the middle and inner ears, since the fibrin adhesive we used is a human product that is immunologically active in the mouse.

ACKNOWLEDGMENTS — Laboratory facilities were provided through the Kresge Foundation, the Louisiana Lions Eye Foundation, and KAM's Fund. Equipment important to this project was provided by Etymotic Research. We thank Dr John K. Cullen, Jr, for his suggestions regarding the formulation of this study and his technical assistance, Dr Charles I. Berlin for his technical assistance and recommendations, Sandra Blanchard and Mary Borden for their help with histologic procedures, Dr Robert Porter for his review of the statistical analyses, and Molly Webster for her assistance with preparation of the manuscript.

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Ann Otol Rhinol Laryngol 97:1988

CHRONIC HERPETIC LARYNGITIS WITH OROPHARYNGITIS

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Chronic herpetic laryngitis, with or without involvement of the oropharynx, is uncommon. We describe a case that was initially diagnosed and treated as squamous cell carcinoma. The subsequent course of the disease, review of the histologic material, and additional laboratory investigation suggested that the lesion was of viral origin and probably was caused by herpes simplex.

KEY WORDS — chronic herpetic laryngitis, chronic herpetic oropharyngitis, squamous cell carcinoma.

According to Pahor,[1] herpetic laryngitis was first described by Meyer in 1879, but recently it has occasioned little comment.[2,3] A review of the past 15 years of periodical literature yielded only a few reports of acute laryngitis caused by herpes simplex and herpes zoster in association with other oropharyngeal lesions.[4-7] Descriptions of chronic herpetic lesions were not found at all.

CASE REPORT

In January 1978, a 63-year-old man developed multiple painful, confluent, shallow yellow ulcerations on the buccal mucosa, tongue, soft palate, and epiglottis and in the postcricoid region. Treatment with amoxicillin and later with nystatin had no effect. One of the buccal lesions was biopsied in April, and the material (specimen 1), though inadequate for histologic examination, showed clusters of dyskaryotic keratinocytes cytologically consistent with squamous cell carcinoma. Biopsy of a tonsillar lesion a few days later (specimen 2) showed inflammation and what was thought to be dysplasia of squamous epithelium. Hematologic investigation, serum electrophoresis, and immunodiffusion were noncontributory, and the patient's serum did not contain anti-basement membrane antibodies. Nevertheless, since the possibility of benign familial pemphigus was entertained, he was given a course of prednisone therapy. The lesions disappeared only to reappear in a few weeks. About 5 months later the patient became hoarse, and during laryngoscopy a nodule was seen on the posterior part of the right vocal cord. Biopsy of it (specimen 3) showed an ulcerative lesion that, in certain respects, simulated squamous cell carcinoma.

Because most pathologists here and consultants elsewhere supported the diagnosis of carcinoma, the patient underwent radiotherapy. The lesion persisted until June 1979, then disappeared. It recurred 12 months later, again in association with lesions in the oropharynx. After that, the lesions appeared and disappeared intermittently; the last episode was without laryngeal involvement and occurred in March 1985. There was no recurrence in 1986.

HISTOLOGY OF SPECIMEN 3

Sections showed the edge of an ulcer with a suprabasal cleft formed by overhanging stratified squamous epithelium and partially lined by atypical basal cells and mononucleated or multinucleated dyskaryotic keratinocytes. The cleft contained similar keratinocytes, mixed with neutrophils, lying free in its space. The ulcer's floor was composed of eosinophilic necrotic material incorporating a few dyskaryotic keratinocytes as well as lymphocytes, histiocytes, and polymorphs. The connective tissue below it was infiltrated by lymphocytes (see Figure; A,B). In one section, the stratified squamous epithelium showed spongiosis, acantholysis, and formation of a suprabasal vesicle containing keratinocytes and polymorphs. The connective tissue below was edematous and infiltrated by a few lymphocytes and histiocytes (see Figure, C). One area of laryngeal mucosa showed crowding and disarray of atypical basaloid squamous epithelium (see Figure, D).

DISCUSSION

The clinical course of the laryngeal lesion was obviously unlike that of squamous cell carcinoma. Its recurrences and its association with oropharyngeal ulcers suggested a chronic inflammatory process. Reexamination of the histologic material supported this view. Although the buccal and tonsillar lesions each showed only a few of the features found in laryngeal biopsy, all were similar. The laryngeal and buccal lesions contained abnormal mononucleated or multinucleated keratinocytes, and that of the tonsil showed spongiosis and basal cell atypia. Presence of a suprabasal vesicle in one of the laryngeal sections suggested that these vesicles were precursors of the ulcers there and in the oropharynx. Therefore, the differential diagnosis should in-

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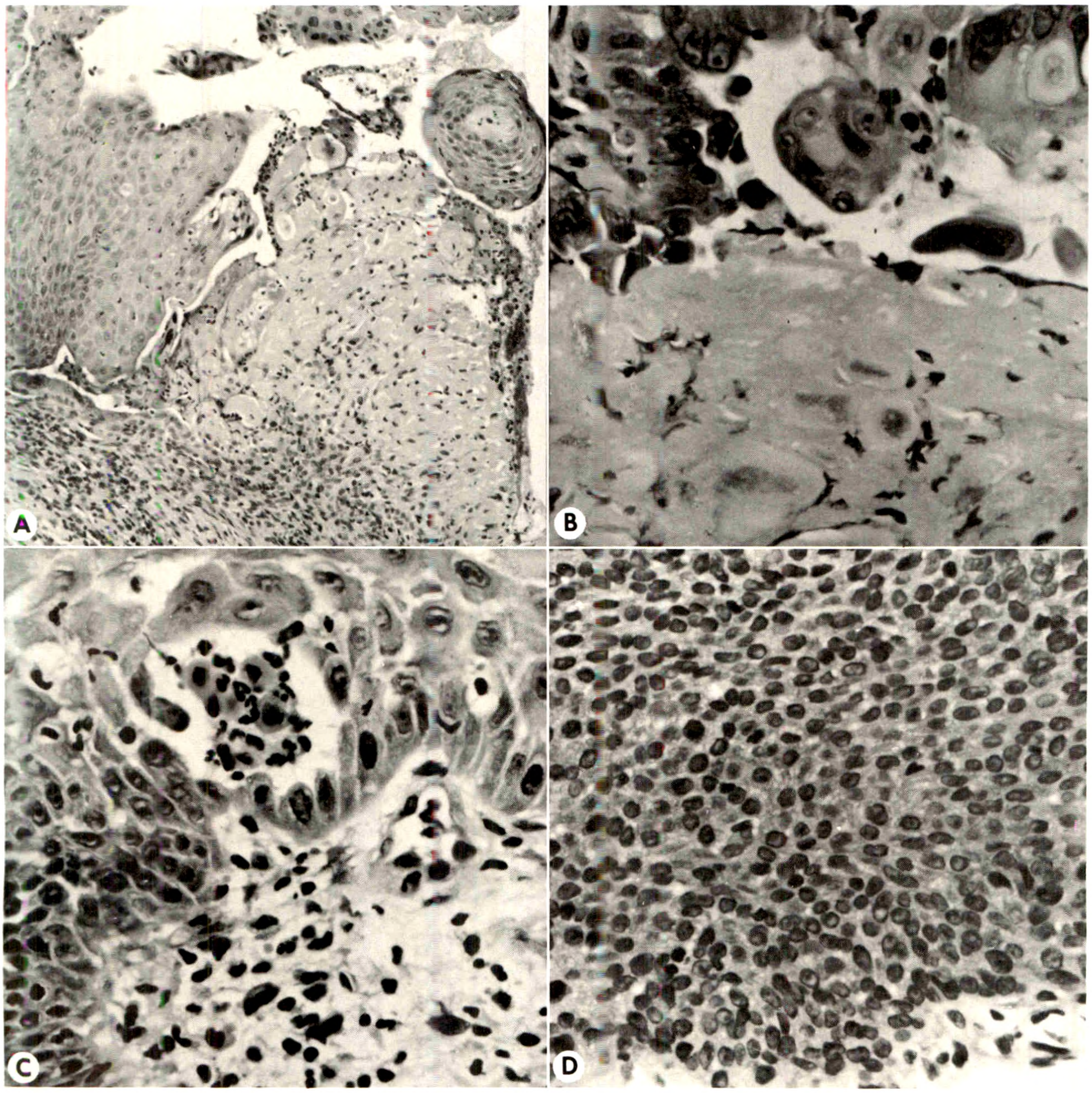

Histologic sections of biopsy specimen 3. A) Cleft at ulcer's edge, formed by overhanging stratified squamous and atypical basal epithelia, contains a few neutrophils and dyskaryotic mononucleated and multinucleated keratinocytes (HES [hematoxylin, eosin, saffron], original x130). Latter are seen also in necrotic tissue of ulcer's floor. Connective tissue below ulcer is infiltrated by lymphocytes. B) Another area of ulcer's edge with dyskaryotic keratinocytes of similar type in cleft and floor (HES, original x590). Atypical basal epithelium is in cleft's corner. C) Spongiosis, acanthosis, some basal cell atypia, and formation of early suprabasal vesicle (HES, original x590). Vesicle contains a few neutrophils and dyskaryotic keratinocytes. Connective tissue below shows minimal mixed inflammatory exudate. D) Area of laryngeal mucosa showing crowding atypical basaloid cells and loss of polarity (HES, original x590).

clude such lesions as pemphigus (vulgaris and vegetans), benign familial pemphigus, erythema multiforme, lichen, and herpes (simplex and zoster).[2,8]

Since the laryngeal lesion displayed intraepithelial vesiculation, familial pemphigus, erythema multiforme, and bullous lichen can be ruled out; their vesicles are subepithelial. Because the lesions lacked eosinophilic infiltrate and their inflammatory reaction was mild, they cannot be considered as those of pemphigus. Also, the immunofluorescent studies were negative for both pemphigus and pemphigoid. Furthermore, none of the above lesions are known to show formation of multinucleated keratinocytes, a feature considered to be pathognomonic for herpetic disease.[9,10] However, subsequent attempts to demonstrate the herpetic antigens by peroxidase-antiperoxidase technique and electron microscopy using portions of unstained paraffin sections were unsuccessful, partly because of the small amount of remaining tissue. Serologic tests at the time of recurrence in 1985 showed convalescent values for both herpes simplex and varicella-zoster groups, and as expected yielded no useful information.[11,12] Viral culture was negative as well. Thus, of necessity, the diagnosis of herpetic disease was made on the basis of light microscopy and clinical course. Since the oropharyngeal lesions were bilateral and were not associated with neurologic symptoms, it seems unlikely that they were caused by herpes zoster virus, leaving herpes simplex as the only alternative.

The literature abounds with descriptions of acute cutaneous herpetic lesions, but contains only a few reports of their occurrence in the larynx.[1,4-7] Chronic laryngeal lesions, with or without oropharyngeal involvement, do not seem to have been either encountered or reported. Chronic cutaneous lesions have been described in both healthy[12] and immunosuppressed individuals.[13,14] There was no clinical or laboratory evidence of immune deficiency throughout the course of this man's illness. It is of interest that initially the lesions in this case seem to have responded favorably to prednisone therapy, though they may have healed in spite of it. More importantly, this case illustrates that the degree of epithelial dyskaryosis in some herpetic lesions may be severe and may lead to the erroneous diagnosis of squamous cell carcinoma and to the wrong therapy.

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VASCULAR EFFECTS OF NEUROPEPTIDES ON NASAL MUCOSA

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We used dog nasal blood vessels and an in vitro muscle tension–detecting technique to examine the vascular effects of several neuropeptides: vasoactive intestinal polypeptide, substance P, neurotensin, somatostatin, and neuropeptide Y (NPY). Electrically induced vasoconstriction was inhibited by every peptide except neurotensin, which enhanced this response. Every preparation treated with somatostatin, and one tissue treated with NPY, showed an enhanced noradrenaline-induced contraction. Only NPY caused a tissue contraction. Preparations precontracted by methoxamine were relaxed by every peptide. These results indicate that all peptides examined have marked but varied vasoactivities.

KEY WORDS — neuropeptides, vascular smooth muscle, vasoconstriction, vasodilatation.

INTRODUCTION

For many years the only autonomic neurotransmitters recognized were acetylcholine (ACh) and noradrenaline (NA). In the 1960s, the existence of nonadrenergic and noncholinergic nerves was clearly established.[1] The suggestion that some nerve cells store and release more than one transmitter was made in 1976.[2] At the present time, a number of biologically active polypeptides are well known as transmitters or modulators of autonomic neurons. In otolaryngology, Uddman et al[3] first demonstrated vasoactive intestinal polypeptide (VIP), one of the neuropeptides, in the nasal mucosa with novel immunocytochemical techniques.

On the basis of the experimental results from such techniques, the schema of the autonomic nervous control of the nose was presented by Änggård[4] in 1983. According to his assumption, VIP and ACh coexist in the parasympathetic neuron and cause vascular dilatation and glandular secretion, while NA and neuropeptide Y (NPY) coexist in the sympathetic neuron and induce vasoconstriction. Substance P (SP) is in the trigeminal sensory neuron and produces antidromic vasodilatation.

Many neuropeptides are known to have powerful vascular actions; however, the responses to such peptides have sometimes been heterogeneous. The aim of this paper is to present various effects of several polypeptides upon the in vitro smooth muscles of the canine nasal blood vessels.

METHOD

We used a technique reported earlier[5] for detecting in vitro muscle tension. After the dog was killed with barbiturate, the nasal mucosa was removed. A tissue strip measuring 5 x 20 mm was suspended in a muscle bath containing Krebs-Ringer solution gassed continuously with 5% CO_2 and 95% O_2. One end of the strip was fixed, and the other was attached to an isometric transducer under a load of 0.5 g. Thus, changes of tissue tension could be recorded (Fig 1). As the contractile tissue is exclusively vascular smooth muscle, the change of tension reflects the contraction or dilatation of vascular smooth muscle cells. As nasal mucosa is known to include several types of blood vessels, such as small arteries, arterioles, capillaries, cavernous sinuses, venules, and small veins, the responses obtained with this preparation should be considered a mixture of the responses of these vessels. Peptides used in this experiment were VIP (Peptide Institute, Japan); SP (Peptide Institute); NPY (Peninsula, Sweden); somatostatin (SS) (Peptide Institute); and neurotensin (NT) (Peptide Institute).

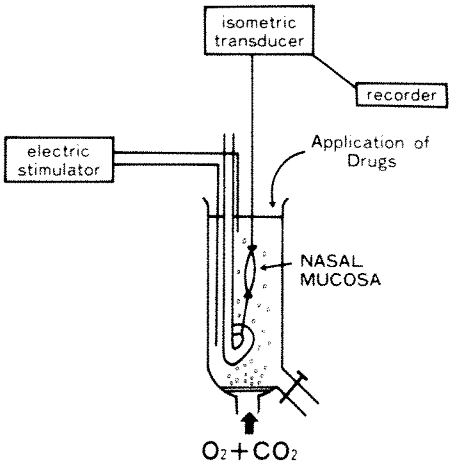

Fig 1. Device for detecting in vitro muscle tension in nasal mucosa. Volume of bath medium is 10 mL.

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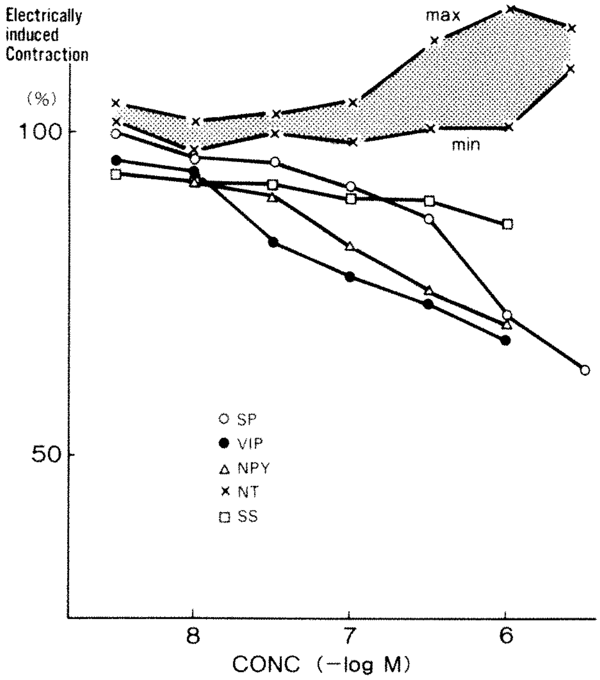

Fig 2. Effect of peptides on electrically induced contraction. Upper curve (max) of neurotensin (NT) shows maximal response when NT is introduced. Lower NT curve (min) depicts value at plateau. Four other peptides (substance P [SP]; vasoactive intestinal polypeptide [VIP]; neuropeptide Y [NPY]; somatostatin [SS]) show dose-dependent inhibition of electrically induced contraction. CONC — concentration.

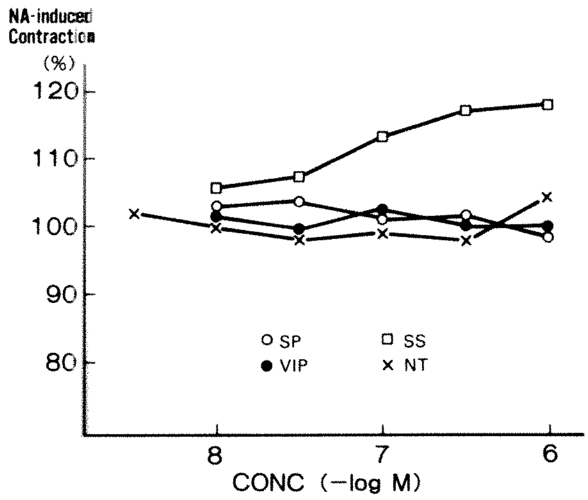

Fig 3. Effect of peptides on noradrenaline (NA)-induced contraction. Only somatostatin augmented response. CONC — concentration.

The following assessments were performed: 1) the effect on electrically induced contraction, 2) the effect on NA-induced contraction, 3) the effect on the resting tension, and 4) the effect on muscle precontracted by methoxamine (MX).

Electrical stimulation was applied transmurally at submaximal intensity (25 V, 5/s, 5 Hz). This stimulation causes NA release from the adrenergic nerve terminal.[6] The released NA occupies postjunctional α-1 adrenoceptors. The stimulation of these receptors not only induces the mobilization of free calcium ions (Ca^{2+}) from the intracellular calcium binding sites, namely, the cell membrane and sarcoplasmic reticulum, but also opens receptor-operating calcium channels to the influx of extracellular Ca^{2+}. The resultant elevation of the intracellular free Ca^{2+} causes a muscle contraction.[7]

Exogenous NA also induces a vasoconstriction through the stimulation of postsynaptic α-adrenoceptors, not only α-1 but also α-2 adrenoceptors situated on muscle cells.[7] Thus, the contraction elicited by exogenous NA is independent of the event at adrenergic nerve terminals.

In order to detect a possible relaxing effect of these peptides, one must precontract the tissue because of the following reasons. 1) Under physiologic conditions, vascular smooth muscles are kept in regular tone by the continuous release of NA from the sympathetic nerve terminals. 2) In our in vitro tension-detecting system, relaxing responses of the muscle in the resting condition cannot be observed, even if the known vasodilators are administered. In the present study, we used 10^{-5} *M* MX as a precontractor.

RESULTS

Effect on Electrically Induced Contraction. After the magnitude of the contraction became stable, a neuropeptide was instilled into the vessel. Figure 2 shows the effect of each peptide on the electrically induced contractions. Except for NT, they inhibited the electrically induced contractions in a dose-dependent manner. When NT was administered, there was first an increased response; then the response gradually decreased to a plateau level. The upper NT curve in Fig 2 shows the initial maximal response, and the lower NT curve shows the minimal value or the response at the plateau.

Effect on NA-Induced Contraction. After the contractile response to 3 x 10^{-6} *M* NA became reproducible, a peptide was introduced before the instillation of NA (n = 5). Somatostatin enhanced the NA response. Vasoactive intestinal polypeptide, SP, and NT did not affect the contractility with NA (Fig 3). Neuropeptide Y was inactive in two preparations and elicited an enhancement in one.

Effect on Resting Tension. Only NPY (> 10^{-7} *M*) produced a contraction of the nasal smooth muscle under the resting tension (Fig 4, bottom). This response was not reversed by rinsing or suppressed by prazosin, an α-1 adrenoceptor blocking agent; however, it was abolished by the absence of Ca^{2+} in the bath medium. As shown in Fig 2, at this concentration NPY caused an inhibition of electrically induced contractions (Fig 4, top).

Effect on Precontracted Preparation. When the nasal mucosa was contracted by 10^{-5} *M* MX, all five

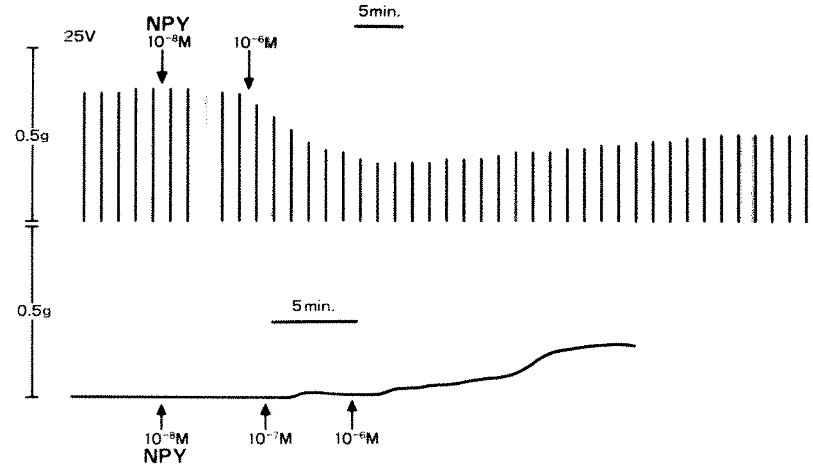

Fig 4. Effect of neuropeptide Y (NPY). In upper graph, NPY inhibits electrically induced contraction in concentration-dependent manner. In lower graph, it contracts tissue under resting tension (0.5 g).

peptides caused it to relax. Substance P and NT were the most effective. This relaxing effect was dose dependent (Fig 5).

DISCUSSION

The history of neuropeptides dawned in 1931, when SP was discovered by von Euler and Gaddum[8]; however, the "peptide era" began as late as the 1970s, when immunohistochemical studies were developed. Peptide research is now one of the fastest-growing areas in medical science. Recent studies have shown that polypeptides are present in certain populations of neurons that also contain classic transmitters.[9]

In addition to the peptides discussed in the Introduction, some peptides recently have been mentioned as coexistent transmitters. Agents such as peptide HI, named on the basis of an NH_2-terminal histidine (H) and COOH-terminal isoleucine (I) amide, are considered to exist in the parasympathetic neuron together with ACh and VIP; and others such as neurokinin A, galanin, and calcitonin gene-related peptide have been regarded as candidates for the coexistent transmitter in the trigeminal neuron with SP. The distribution of these substances in each neuron was established by Uddman and Grenner.[10]

The idea of prejunctional and postjunctional receptors is widely accepted at present. There are some prejunctional receptors known to modulate the NA release from sympathetic nerve terminals. For example, α-2 adrenoceptors and muscarinic cholinoceptors inhibit NA release, while β-2 adrenoceptors enhance it. When contractions induced by both electrical stimulations and NA are depressed in the presence of any substance, the site of its action must be postjunctional. However, if only the former contraction is inhibited, as seen in the present study, the idea of prejunctional inhibition of NA release is supported. Also, in the relaxation of precontracted tissues, the site of the action must be on the receptors of the effector organ, either of the smooth muscle cell itself or of the endothelium, which has been shown to produce endothelium-derived relaxing factor, which can relax smooth muscles.[11]

Vasoactive Intestinal Polypeptide. Vasoactive intestinal polypeptide is a 28–amino acid peptide and is widely distributed in the central and peripheral nervous systems. In nasal mucosa, VIP-immunoreactive nerves were identified around glands and blood vessels.[3] These VIP-immunoreactive neurons have been confirmed to correspond to parasympathetic postganglionic neurons.[12] The coexistence of ACh and VIP in the nose has been well established.[13] Vasoactive intestinal polypeptide is responsible for atropine-resistant vasodilatation. The following dual vasodilator mechanism of ACh and VIP has been demonstrated in nasal blood vessels.[13] Electrical stimulation of the parasympathetic nerve induces vasodilatation. At low frequencies, the vasodilator response may be due to ACh, while the con-

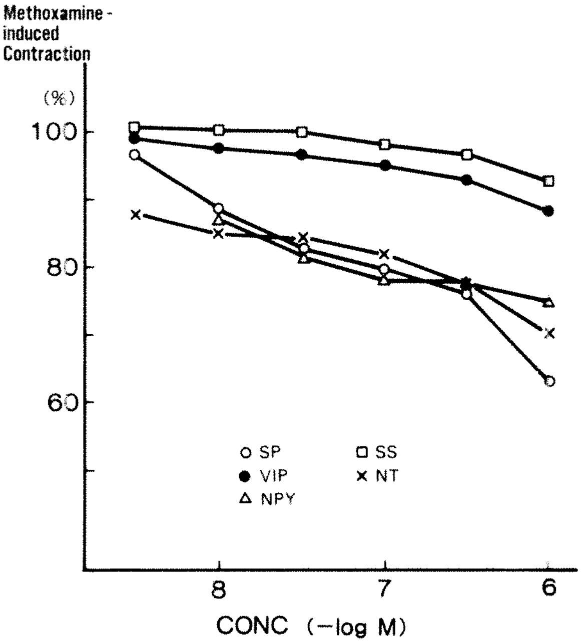

Fig 5. Effects of peptides on tissue precontracted by methoxamine. All peptides relaxed tissue in dose-dependent manner. Somatostatin and VIP show minimal relaxing effect. CONC — concentration.

	SP	VIP	NT	SS	NPY
Electrically induced Contraction	⇩	⇩	⬆	⇩	⇩
NA-induced Contraction	—	—	—	⬆	—~⬆
Precontracted Condition by MX	⇩	⇩	⇩	⇩	⇩
Resting Condition	—	—	—	—	⬆

Fig 6. Effect of peptides on nasal blood vessels. They relax or inhibit response (↓); contract or augment response (↑); or have no effect (–).

tribution by VIP increases with the stimulation frequency. Exogenous VIP causes a dose-dependent relaxation in various vasculatures. This response has been regarded to be a direct receptor-mediated effect on smooth muscles, and it seems to be in accordance with increased cyclic AMP.[14] In the present study with nasal mucosa, such a relaxing response was clearly recognized in the preparation precontracted by MX. The inhibitory effect on electrically induced contraction also was observed in the present study. On the basis of a previous study, this effect has to do with prejunctional receptors.[6,7] However, the measurement of released NA was not performed simultaneously at this time. No modulatory effect of VIP upon NA-induced contraction was recognized in this experiment.

Neuropeptide Y. Neuropeptide Y recently was isolated from porcine brain.[15] Soon after, the coexistence of NA and NPY was established.[16] In the periphery, only a portion of the sympathetic neurons seem to contain NPY. These neurons may innervate specific target tissues such as arteries, arterioles, or the vas deferens. There seem to be none or only a few NPY fibers around veins.[16] Peripheral sympathetic neurons innervating structures other than the arterial system or vas deferens may contain other peptides. The heterogeneity of the response by exogenous NPY may reflect the difference of the distribution of the receptors involved. Neuropeptide Y itself is known to cause a tissue contraction.[17] According to Ekblad et al,[18] NPY caused a marked vasoconstriction in the femoral vein, but induced a far smaller response in the femoral artery of guinea pigs and rats. No response was detected with human specimens. It is postulated that in cerebral arteries and peripheral veins, which are equipped with α-2 adrenoceptors or a population of mixed α-1 and α-2 adrenoceptors, NPY causes a constriction, while in vessels with a strict population of α-1 receptors, such as the muscular arteries, NPY potentiates the NA response.[19] If this assumption is true, the inconsistency of the enhancing effect and the clear vasoconstriction shown in the present study are elucidated by our former work. We showed that nasal smooth muscle of the dog has both α-1 and α-2 adrenoceptors.[7] The fact that the preparations used in this experiment were not single vessels but nasal mucosae that contained various types of blood vessels also may explain the inconsistent enhancing response.

Most investigators insist that NPY augments the electrically induced response on the vascular smooth muscle. In this situation, the amount of released NA was not increased.[18] Hence, this enhancing effect is considered to be postjunctional. The inhibitory effect of NPY upon the electrically induced contraction as presented in this study has not been reported yet in vascular smooth muscle, although such an inhibition was documented in the vas deferens.[16] At present we have no good evidence to explain the discrepancy. However, our data point toward prejunctional inhibitory NPY receptors in the noradrenergic nerve terminals of the canine nasal mucosa.

Substance P. It has been known for over 80 years that an antidromic stimulation of sensory nerves induces a local vasodilatation in several tissues. Substance P is now regarded as a mediator of this response. According to in vitro studies on vasoactivity of SP, SP relaxes precontracted vascular tissues, either veins or arteries. However, the mechanism of this response was thought to be different for each. Substance P may work directly on muscles of veins, while on arteries it may stimulate the endothelium to produce endothelium-derived relaxing factor, which causes a smooth muscle relaxation.[20] In rabbit aortas and rabbit mesenteric veins, SP was reported to cause contraction.[21] However, such a contractile response was not seen in the present study. We saw the inhibitory effect on electrically induced contraction probably due to prejunctional SP receptors, and the relaxing effect upon MX-induced contraction.

Somatostatin. Somatostatin is known to coexist with NA in sympathetic ganglia of guinea pigs. It was discovered recently in the sphenopalatine ganglion of the dog.[22] However, the interrelationship between SS and NA in the nasal mucosa has not been discussed. The fact that SS enhanced the NA-induced contraction may provide the clue to elucidating this problem. The vasodilating action of SS recognized in the present experiment was rather poor. In vitro vasodilatation also has been recognized in mesenteric vessels, both arteries and veins.

Neurotensin. Neurotensin has not been identified in nasal tissues. The coexistence with NA has been shown only in adrenal medulla. In dogs, NT is a systemic vasoconstrictor,[23] while it is known to cause vasodilatation in anesthetized rats. The potentiating effect of NT upon electrically induced contraction of the mouse vas deferens, although not of the vascular smooth muscle, has been described by Allen et al.[24] The dual effect we obtained, that is, a rapid enhancement and a subsequent slight relaxation, may be regarded as due to the short activity of this material.

CONCLUSION

The results of the present investigation are summarized as Fig 6. It suggests that the actions of these peptides are too complex for us to provide a simple model of the peptidergic system in the dog nasal mucosa. Substance P is supposed to work as a vasodilator, not only by inhibition of NA release from nerve terminals, but also by direct action on the effector organ. Vasoactive intestinal polypeptide might have the same property. Neurotensin enhances the NA release from nerve endings. It also can relax the precontracted tissues in a direct manner. Somatostatin augments the NA-induced contraction. Neuropeptide Y can contract vascular smooth muscle cells, while it suppresses NA release from nerve endings and relaxes precontracted smooth muscles.

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Ann Otol Rhinol Laryngol 97:1988

IN VITRO ELECTROPHYSIOLOGIC STUDIES ON NASAL AIRWAY RECEPTORS OF THE RABBIT

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Rabbit nasal airway receptors were investigated electrophysiologically in vitro. Cold receptors, warm receptors, and mechanoreceptors were found in the nasal membrane. The cold receptors showed a maximum static discharge at 28°C, and the warm receptors at 38°C. These thermoreceptors were activated constantly at temperatures between 18°C and 40°C. The mechanoreceptors were seen to adapt rapidly to gentle mechanical stimulation and were activated easily by repeated stimuli. Air blown directly at the nasal membrane did not activate the mechanoreceptors. It was concluded that nasal airflow sensation is due mainly to the activation of cold or warm receptors in the nasal airway, rather than the stimulation of mechanoreceptors.

KEY WORDS — cold receptors, mechanoreceptors, nasal airflow sensation, posterior nasal nerve, warm receptors.

INTRODUCTION

Because it is difficult to excise and prepare intact nasal afferent fibers from experimental animals for electrophysiologic studies, no evidence has been published as yet that proves the existence of specific groups of nasal airway receptors, which are thought to include thermoreceptors, mechanoreceptors, and polymodal receptors.

The conditioning of inspiratory air seems to be controlled partly by afferent discharges from nasal airway receptors. Clinical reports have stated that a sensation of increased nasal patency in humans is derived from a stimulation action or sensitizing effect on cold receptors of the nasal membrane.[1] In animal experiments, mechanical, chemical, and electrical stimulation of the nasal membrane, which is mediated by specific groups of receptors, has elicited cardiovascular and pulmonary reflexes.[2-4]

At present, electrophysiologic confirmation of the presence of nasal airway receptors is a fundamental problem that must be solved if nasal physiology and clinical practice are to progress. In this study, the properties of nasal airway receptors were investigated by means of an electrophysiologic technique.

MATERIALS AND METHODS

Eight adult male rabbits were anesthetized by intraperitoneal injection of urethane (1 g/kg), and the trachea was cannulated. The body of the zygoma, portions of the zygomatic arch, and the orbital contents were resected. The posterior nasal nerve trunk was found to be attached to the pterygopalatine ganglion, and the maxillary nerve was identified in the orbit. The posterior nasal nerve trunk was seen to pass immediately through the sphenopalatine foramen and to innervate the lower parts of the ipsilateral nasal cavity.

The posterior nasal nerve trunk and the entire nasal cavity were removed intact from the rabbit. The ipsilateral nasal cavity was opened into a plane, including the lower parts of the nasal septum and the lateral wall. The posterior nasal nerve trunk was placed in a recording chamber, and the nasal membrane, along with the nasal septum and lateral wall, was placed in an adjoining stimulation chamber (Fig 1). The posterior nasal nerve trunk was dissected into fine filaments. Afferent discharges were picked up by an Ag-AgCl bipolar electrode under paraffin oil. Another Ag-AgCl bipolar electrode was used in several experiments for electrical stimulation in order to measure conduction velocities, which were determined by calculating the distance between the two electrodes and the delay time between the stimulation artifact and the afferent discharge.

The surface of the nasal membrane and its reverse side were superfused separately with Krebs-Ringer solution in the following manner (m*M*): a solution of sodium chloride (111), sodium glutamate (14.7), sodium hydrocarboxide (25.6), potassium chloride (4.7), calcium chloride (2.2), magnesium chloride (1.1), and glucose (5.6) was applied; and the mixture was gassed with 95% O_2 and 5% CO_2. The pH was adjusted to 37°C with 5 m*M* HEPES buffer (Nakarai Chemical Ltd). The reverse side of the membrane was maintained at a temperature of 36.5°C±0.3°C, and the flow rate of the solution was 2 mL/min. The temperature of the surface of the nasal membrane was allowed to increase slowly from 18°C to 40°C over a period of about 13 minutes by controlling the temperature of the superfused solution. Temperature was recorded by means of a small thermistor mounted directly on the

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been elicited by mechanical stimulation of the nose.[2] These reflexes seem to be mediated by the nasal airway mechanoreceptors.

Burrow et al[1] have reported that several aromatic substances fail to change airflow resistance although they produce a sensation of increased nasal patency by stimulation action or a sensitizing effect on cold receptors of the nasal membrane. Cole and Haight[12] have reported that local anesthesia of the nasal membrane in humans causes a slight sensation of stuffiness without causing any change in nasal airflow resistance. From the results of the present study, it is possible to say that nasal airflow sensation is due mainly to the activation of cold or warm receptors rather than that of mechanoreceptors. However, it is still a matter of speculation whether or not certain aromatic substances directly or indirectly stimulate the warm receptors and mechanoreceptors as well as cold receptors. In the epipharynx, it has been concluded by Nail[13] that various irritants and antigenic agents alter nasal mechanosensitivity.

In a histologic investigation carried out by Cauna et al,[14] the receptors of the nasal membrane were thought likely to be free nerve endings, which are all of one kind and simple in structure. However, the question still exists as to whether the receptors studied electrophysiologically are the same as those seen by histologic observation.

At present, it may be stated that nasal airway thermoreceptors and mechanoreceptors play an important role in the normal pattern of breathing, including the conditioning of air entering the nose. It is concluded that thermoreceptors and mechanoreceptors exist in the nasal membrane and that the nasal airflow sensation is due mainly to the activation of cold or warm receptors in the nasal airway, rather than stimulation of mechanoreceptors. However, further study is needed to classify these receptors more precisely into specific groups.

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Ann Otol Rhinol Laryngol 97:1988

EFFECTS OF BACTERIAL ENDOTOXIN ON CILIARY ACTIVITY IN THE TUBOTYMPANUM

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The discovery of endotoxin in effusion of otitis media with effusion (OME) has suggested the possibility that bacterial endotoxin may be involved in the pathogenesis and development of OME. In this study, we investigated the direct effects of lipopolysaccharide (LPS), possessing the major part of endotoxin activity, on the ciliary activity in the tubotympanum. The study shows that LPS deteriorates ciliary activity in a dose-response fashion and that even low levels can, with extended exposure, cause dysfunction of cilia. It can be postulated that endotoxin in middle ear effusions aggravates the condition of mucociliary dysfunction, thus leading to chronic OME.

KEY WORDS — ciliary activity, lipopolysaccharide, tubotympanum.

INTRODUCTION

In our previous studies,[1,2] evidence was presented that the lining of the tubotympanum in its normal state exhibits ciliary activity similar to that in the respiratory mucosa. Our recent studies on some diseased middle ear linings have demonstrated the possibility that the ciliary activity in the tubotympanum may be involved in the manifestation of various middle ear diseases, including otitis media with effusion (OME).[3-5] In this experimental study, we examined the effects of bacterial lipopolysaccharide (LPS) on ciliary activity in the tubotympanum.

MATERIALS AND METHODS

Twenty-four guinea pigs (250 g) with normal pinnal reflexes were killed. Mucosal samples from three sites in the right tubotympanum were obtained from each animal (site A, mucosa from the bony portion of the eustachian tube; site B, middle ear mucosa close to the tubal orifice; site C, middle ear mucosa more distal to the orifice than site B; Fig 1). These samples were put into sealed chambers, each containing 3 mL of physiologic saline solution. First, the baseline ciliary activity (beats/minute) was determined at an ambient temperature of 30°C according to the direct and quantitative photoelectric method of Ohashi and Nakai.[6,7] The physiologic saline solution was expelled and replaced immediately with saline solutions containing various concentrations of lipopolysaccharide (LPS) of *Klebsiella pneumoniae* (Sigma). Samples from eight animals were examined for ciliary activity in a 10-μg/mL LPS solution. Another two sets of eight samples were examined in solutions of 100 μg/mL and 1,000 μg/mL of LPS, respectively. The ciliary activity of all three sets of samples was examined at intervals of 5, 10, 15, 20, 25, 30, 40, 50, and 60 minutes after replacement, using the same photoelectric method. Any change in ciliary activity was expressed as a percent deviation from the baseline level recorded in the physiologic saline solution.

RESULTS

Effects of 10-μg/mL LPS Solution. The ciliary activity of site A increased rapidly in the first 5 minutes, then gradually returned to the baseline level, reaching it at 30 minutes. Then it gradually slowed down, but the cilia remained quite active, even at 60 minutes. The changes in ciliary activity of site B were similar to those of site A: ciliary activity was more frequent for the first 25 minutes, then it returned to its baseline level by 30 minutes. After that, it decreased gradually to 78.6% ±8.0% of the baseline level at 60 minutes. Ciliary activity of site C declined linearly, and all activity ceased within 25 minutes (see Table and Fig 2A).

Effects of 100-μg/mL LPS Solution. Ciliary activity of site A slowed down steadily, but ciliated cells from this site continued to beat even after 60 minutes, when the recorded ciliary activity was about 40% under the baseline level. The changes in ciliary activity of site B showed a close resemblance to those of site A. The ciliary activity of site C declined markedly: it was down by about 40% at 5 minutes, 60% at 10 minutes, and 90% at 15 minutes. All cilia examined in this site ceased moving within 20 minutes (see Table and Fig 2B).

Effects of 1,000-μg/mL LPS Solution. The ciliary activity of site A gradually became less frequent. It

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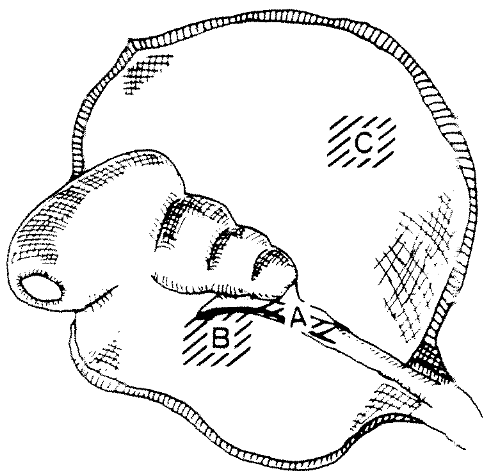

Fig 1. Locations for biopsy specimens. A — eustachian tube mucosa, B — middle ear mucosa proximal to eustachian tube, C — middle ear mucosa distal to eustachian tube.

was down by about 20% after 5 minutes and decreased gradually thereafter, ceasing completely within 50 minutes. The changes in ciliary activity of site B were very similar to those of site A. By contrast, no ciliary activity of site C was recorded at 5 minutes; in fact, ciliary activity was observed by phase-differential microscopy to stop within 3 minutes (see Table and Fig 2C).

DISCUSSION

Otitis media with effusion has been considered a noninfectious condition caused by tubal obstruction or allergy.[8-10] Data of Senturia et al,[11] however, and those of recent studies have demonstrated that 22% to 77% of cases show culturable bacteria.[12-22] Evidence has been mounting that bacterial involvement may be one of the major responsible pathogenetic factors in the manifestation and development of OME. Using the limulus amebocyte lysate (LAL) assay, Bernstein et al[23] demonstrated that middle ear effusions (MEEs) from three of 17 cases contained endotoxin. Using a similar assay, DeMaria et al[24] examined the MEEs from 89 children with chronic OME. They reported that 71 of the samples (80%) exhibited endotoxin activity in concentrations ranging from 0.5 to more than 512 ng/mL, and that endotoxin also was present in 67% of the culture-negative MEEs. These reports on the discovery of endotoxin in MEEs from patients with chronic OME suggest the possibility that endotoxin may be involved in the pathogenesis of OME. Furthermore, DeMaria et al[25] observed clear, amber-colored MEEs in the chinchilla after injection of killed *Hemophilus influenzae* organisms or endotoxin purified from these bacteria in the tubotympanum. Their results support the possibility that bacterial endotoxin is responsible for effusion production. The major mechanism involved could be the increased vascular permeability in the middle ear due to bacterial endotoxin, even if the bacteria are no longer viable in the middle ear.

Another mechanism involved could be the dys-

CHANGES IN CILIARY ACTIVITY AS PERCENT DEVIATION (MEAN ± SD) FROM BASELINE

			Middle Ear Mucosa	
Solution	*Time (min)*	*Eustachian Tube Mucosa (N = 8)*	*Proximal to Tube (N = 8)*	*Distal to Tube (N = 8)*
10 μg/mL lipopolysaccharide	5	125.4 ± 7.8	122.6 ± 5.9	65.0 ± 8.5
	10	124.4 ± 5.9	123.5 ± 6.6	48.3 ± 14.1
	15	125.5 ± 6.6	122.7 ± 6.3	18.4 ± 14.1
	20	115.3 ± 7.6	118.2 ± 7.2	8.9 ± 11.2
	25	112.7 ± 6.8	114.4 ± 6.3	0.0 ± 0.0
	30	101.2 ± 5.6	99.8 ± 6.5	0.0 ± 0.0
	40	90.2 ± 7.1	91.5 ± 6.3	0.0 ± 0.0
	50	85.4 ± 8.8	84.4 ± 7.9	0.0 ± 0.0
	60	80.5 ± 7.7	78.6 ± 8.0	0.0 ± 0.0
100 μg/mL lipopolysaccharide	5	93.1 ± 4.1	94.8 ± 4.3	58.3 ± 7.9
	10	87.3 ± 3.8	90.2 ± 4.2	37.6 ± 9.8
	15	84.9 ± 5.7	86.7 ± 4.1	8.2 ± 15.0
	20	80.2 ± 7.2	82.3 ± 5.8	0.0 ± 0.0
	25	77.5 ± 7.6	76.8 ± 7.6	0.0 ± 0.0
	30	75.4 ± 7.4	75.4 ± 7.5	0.0 ± 0.0
	40	70.3 ± 6.8	70.2 ± 8.2	0.0 ± 0.0
	50	67.4 ± 5.8	66.8 ± 7.3	0.0 ± 0.0
	60	62.5 ± 7.7	63.1 ± 7.7	0.0 ± 0.0
1,000 μg/mL lipopolysaccharide	5	83.3 ± 6.5	80.1 ± 7.6	0.0 ± 0.0
	10	76.4 ± 5.8	74.6 ± 8.8	0.0 ± 0.0
	15	68.3 ± 7.6	70.3 ± 9.6	0.0 ± 0.0
	20	56.8 ± 8.3	61.4 ± 12.3	0.0 ± 0.0
	25	40.2 ± 7.4	41.4 ± 9.6	0.0 ± 0.0
	30	37.6 ± 9.5	35.5 ± 8.8	0.0 ± 0.0
	40	27.1 ± 17.1	27.3 ± 15.8	0.0 ± 0.0
	50	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
	60	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0

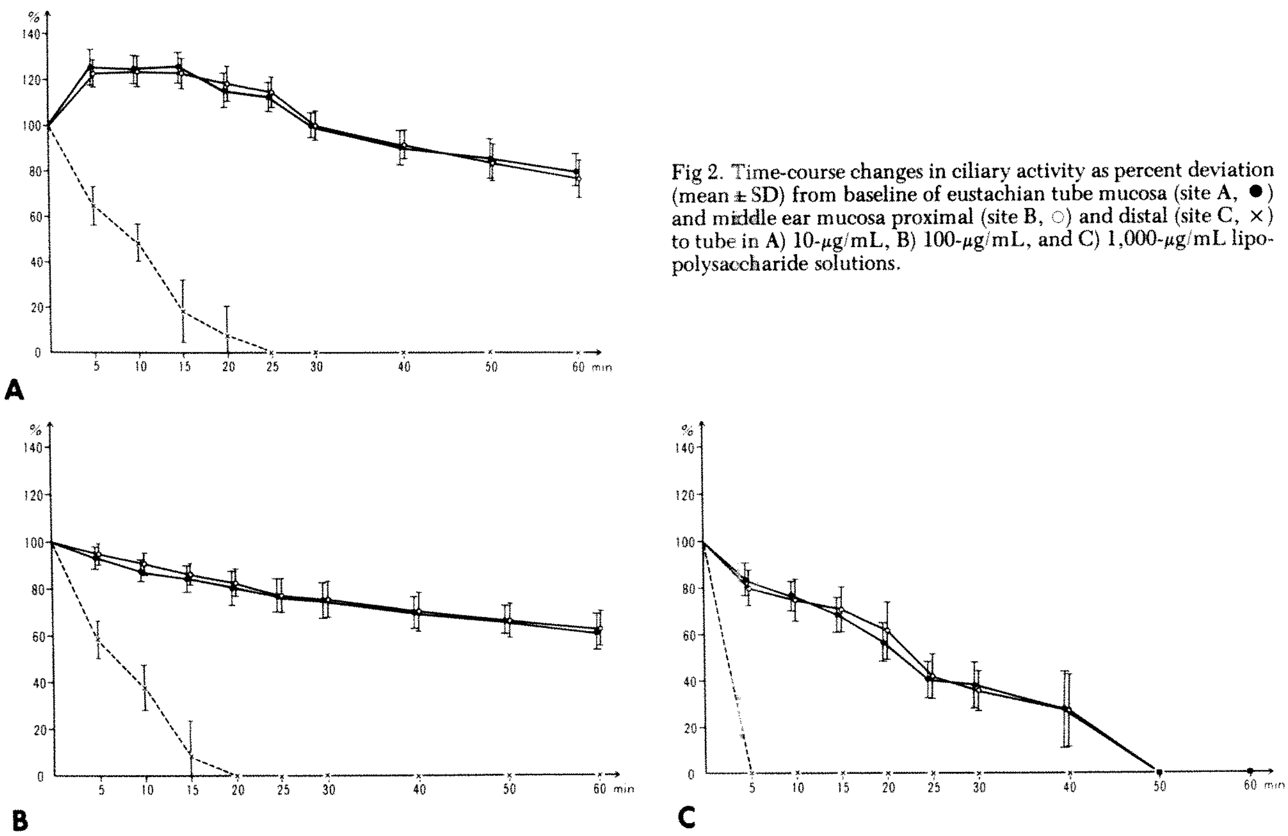

Fig 2. Time-course changes in ciliary activity as percent deviation (mean ± SD) from baseline of eustachian tube mucosa (site A, ●) and middle ear mucosa proximal (site B, ○) and distal (site C, ×) to tube in A) 10-μg/mL, B) 100-μg/mL, and C) 1,000-μg/mL lipopolysaccharide solutions.

function of the mucociliary system. If the mucociliary system is functioning effectively, the effusion formed in the middle ear is cleared through the eustachian tube. The exact mechanism by which effusion fails to be cleared via a patent eustachian tube has not been thoroughly investigated.

Morphologic studies have established that the middle ear lining has a mucociliary system and that it plays an important role in the defense system of the tubotympanum.[26-30] Sadé[31] has demonstrated, by tracing the movement of foreign materials placed on the mucosa, that the middle ear mucosa has an active transport function. Our series of recent studies[1-5] using a photoelectric method has confirmed that this clearance is carried out by cilia. We also disclosed the involvement of some pathologic factors in dysfunction of cilia in the tubotympanum.

In this study, we examined the hitherto unknown effects of LPS, possessing the major part of biologic activity of endotoxin, on ciliary activity in the tubotympanum. Our results show clearly that LPS deteriorates the ciliary activity in a dose-response manner, and that even low levels can, with extended exposure, cause dysfunction of cilia. Such remarkable effects were observed on the cilia located in the portion distal to the tubal orifice. It is possible that endotoxin is more difficult to expel from the tubotympanum when ciliary activity has already been damaged by preceding pathologic factors, and it may be present for a prolonged period in the tympanic cavity, thus worsening the condition of the mucociliary system.

This is the first experimental study that has investigated endotoxin involvement in the pathogenesis of OME, focusing on the effects of endotoxin on ciliary activity in the tubotympanum. The present study, however, is preliminary, and it contains some technical problems to be improved in the future. We used LPS derived from *K pneumoniae* in this study. Although endotoxins share many universal biologic properties, there are some differences in composition that influence antigenicity. Further study using endotoxin derived from pathogenic organisms such as *H influenzae* will be necessary. The technique we used affords examination of the effects of LPS on ciliary activity for a maximum of 60 minutes. Further study using a technique of tissue culture may be necessary to evaluate its long-term effects on the mucociliary system. We chose three concentrations of LPS (10, 100, and 1,000 μg/mL). Further study using smaller concentrations of LPS will be more significant, because the concentrations of LPS detected in human effusions are smaller.

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Ann Otol Rhinol Laryngol 97:1988

EPITHELIAL DISTRIBUTION IN THE HUMAN FETAL LARYNX

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Scanning and transmission electron microscopy and light microscopy were used to study the distribution of squamous epithelium and ciliated respiratory type epithelium in ten midtrimester human fetal larynges. Particular attention was paid to the subglottic region, where previous studies have reported areas of squamous metaplasia in neonates, infants, and nonsmoking adults. Both types of epithelium were found in different proportions in the supraglottic, glottic, and subglottic regions. There was considerable downward extension of squamous epithelium from the glottis into the subglottic region, with a wide transition zone where both types of epithelium were found in close association. These observations would suggest that such areas of squamous epithelium in the nonglottic larynx are normal, rather than always indicating a response to extrinsic trauma or irritation. Therefore, the term squamous metaplasia may be inappropriate when applied to such areas in the adult larynx.

KEY WORDS — epithelium, fetus, squamous metaplasia, subglottic region.

INTRODUCTION

Following birth, the human larynx is subjected to a variety of traumas, such as the mechanical effects of phonation, dusts, and tobacco smoke. Any histologic study of the larynx must take these factors into account. In the fetus, however, the larynx can be regarded as being free from such traumas. Therefore, a knowledge of the epithelial distribution in the fetal larynx would provide a valuable baseline of laryngeal epithelial morphology with which both normal and diseased adult laryngeal epithelium could be compared. The significance of such traumas then could be assessed. It also would provide information about changes in epithelial distribution that occur as a result of normal growth.

The first study of the epithelium of the human fetal larynx was undertaken by Tourneux in 1885.[1] There have been few similar studies since then, and these often have been limited in their observations.[2,3] The numbers of fetal larynges studied have been small, and only light microscopy has been used to look at the epithelium. The small numbers may reflect the difficulty of obtaining suitable material, a serious problem in this area of research. The subglottic region of the larynx has received a great deal of attention recently in relation to squamous metaplasia. Islands of squamous epithelium were noted in this area first by Heymann[4] and Kanthack[5] in 1889 and subsequently by others.[6,7] Many people have regarded these areas as being of pathologic significance, and an association between smoking and subglottic squamous metaplasia has been established.[8] A recent study using a macroscopic surface staining technique to differentiate between squamous and respiratory epithelium even found areas of squamous metaplasia in the subglottic regions of neonates and stillborn infants.[9] It was felt that a further study of this region of the larynx in the human fetus might help to elucidate the significance of these areas and settle the question of whether they represent pathologic or physiologic metaplasia,[2] or whether they need be regarded as areas of metaplasia at all.

MATERIALS AND METHODS

The larynges were removed from ten midtrimester human fetuses of between 14 and 18 weeks' gestational age (as assessed by ultrasound scanning and the date of the last menstrual period). The abortions were not for fetal abnormalities, and they were induced using only prostaglandin E. In terminations where hypertonic urea had been used, the material obtained was unsuitable for microscopy because of early intrauterine death and gross epithelial disruption resulting from the urea.

Each larynx was fixed in 2.5% glutaraldehyde in 0.1 *M* cacodylate buffer at pH 7.3 within 40 minutes of the termination. Fixation was at room temperature for a maximum of 3 hours. Seven of the ten specimens were sectioned along the midline sagittal plane (Fig 1A); the other three were sectioned coronally through a point halfway along the length of the true vocal cord. Attempts to differentiate squamous from respiratory epithelium using surface dye techniques[10] were unsuccessful because of the small size of the specimens. Following primary fixation, specimens were postfixed in 2% osmium in cacodylate buffer and prepared for scanning electron microscopy (SEM). To provide a conductive coat, each was processed using the osmium-thiocarbohydrazide-osmium-thiocarbohydrazide-osmium (OTOTO) technique of Malick and Wilson.[11] Then each specimen was critical point dried (Polaron E3000) using carbon dioxide and examined in a JEOL 35C scanning electron microscope. We have noted less tissue distortion with this technique than with more conventional

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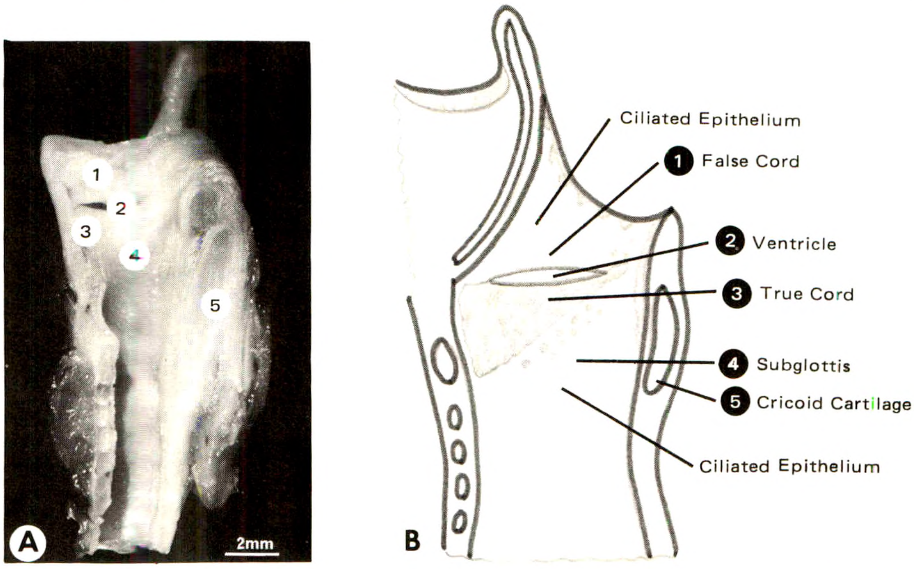

Fig 1. Fetal larynges. A) Sagittal section through larynx of 16-week human fetus (original x8). B) Diagram showing ciliated and squamous nonciliated (shaded areas) of fetal larynx.

methods of preparation. It also allows subsequent thin sectioning of samples following SEM.[12] Consequently, after SEM, each specimen was placed in 100% ethanol, and any areas of interest were dissected out and embedded in Araldite in preparation for thin sectioning. Sections were examined using a JEOL 100S transmission electron microscope (TEM).

Because of its small size, it was usually possible to mount the entire hemilarynx intact for SEM, thereby overcoming the difficulties of surface orientation that can occur after dividing a specimen into smaller pieces.

The 20 hemilarynges studied by SEM all showed the same general pattern of epithelial distribution, although the ratio of the two epithelial types appeared variable in certain areas. There were no significant differences between larynges of different gestational ages. When there was any doubt as to the type of epithelium in any region, the tissue was dissected, sectioned, and examined by TEM. Six of the subglottic specimens were sectioned for this purpose. The epithelial distribution in each of the anatomic regions of the larynx will be discussed in turn.

Glottis. Figure 2A shows the true and false vocal cords with the intervening ventricle. In each fetus, the true cord was covered by nonciliated epithelium with the surface characteristics of squamous epithelium. These included a pavementlike surface contour, intercellular boundaries marked by slightly elevated ridges, and a fingerprint pattern of surface microridges.[13] Examination by TEM confirmed this as squamous epithelium by demonstrating the presence of desmosomes and tonofibrils (Fig 2B). In eight of the larynges, single ciliated cells were scattered along the entire length of the true cord. At the anterior commissure, a narrow vertical band of ciliated cells was present in two of the three coronally sectioned larynges. At the posterior commissure of all three of these larynges, a strip of squamous epithelium extended from the interarytenoid notch down into the subglottic region. The fingerprint surface of such cells is well shown in Fig 2C. Examination by TEM again confirmed the squamous origin of the epithelium by demonstrating desmosomes and tonofibrils. Immediately lateral to this squamous strip, flanking it on either side, was a band of ciliated mucosa.

The inaccessibility of the laryngeal ventricle meant that only the medial portion of the ventricular floor could be studied by SEM. This area consisted of a narrow transition zone between the squamous type of epithelium of the glottis and the ciliated respiratory type of mucosa found more laterally on the floor of the ventricle, as seen by light microscopy study of the coronally sectioned larynges.

Supraglottic Region. The surfaces of the false vocal cords were covered almost entirely by ciliated cells typical of those found in respiratory mucosa. Scattered goblet cells and microvillar cells also were noted, but there was a marked absence of surface mucus from all of the larynges. The mucosa over the posterior surface of the epiglottis was very similar in appearance to that of the false vocal cords (Fig 2A). The free edges of the epiglottis and aryepiglottic folds, however, were made up of a combination of both epithelial types in close association (Fig 3); their ciliated respiratory and squamous origins were confirmed by TEM examination. On the lingual surface of the epiglottis, the epithelium was entirely squamous.

Subglottic Region. The subglottic region was defined as that area of the larynx below the free edge of the true vocal cord and above the lower border of the cricoid cartilage. An alternative definition, which describes its upper border as the point where the squamous epithelium of the true vocal cord reaches its inferior extent, was shown by this study to be too variable to use as a guideline. It is also clinically impractical.

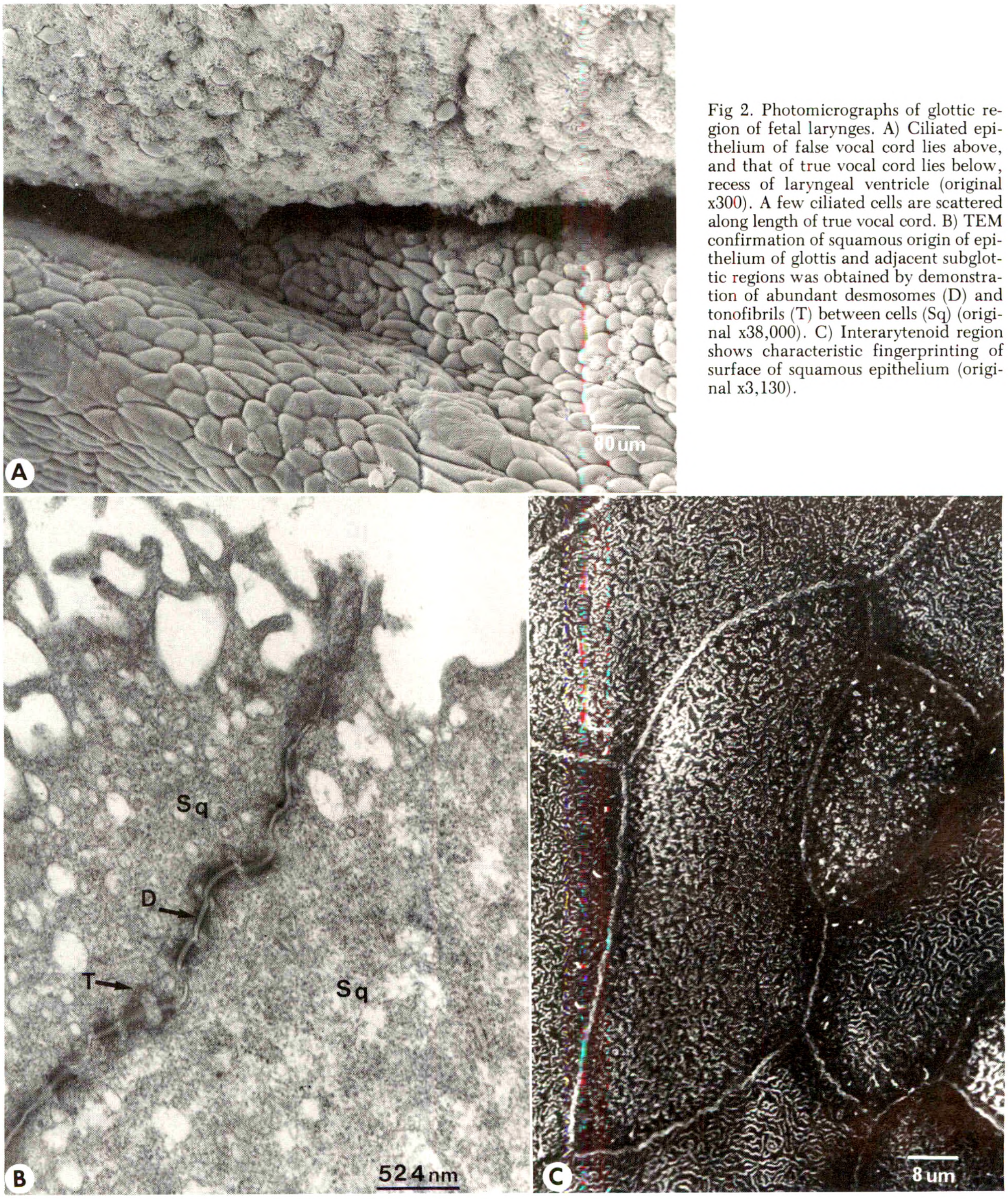

Fig 2. Photomicrographs of glottic region of fetal larynges. A) Ciliated epithelium of false vocal cord lies above, and that of true vocal cord lies below, recess of laryngeal ventricle (original x300). A few ciliated cells are scattered along length of true vocal cord. B) TEM confirmation of squamous origin of epithelium of glottis and adjacent subglottic regions was obtained by demonstration of abundant desmosomes (D) and tonofibrils (T) between cells (Sq) (original x38,000). C) Interarytenoid region shows characteristic fingerprinting of surface of squamous epithelium (original x3,130).

The greatest variation in the distribution of the two epithelial types was noted in the subglottic region. In all cases, the downward extension of squamous epithelium from the glottis into the subglottic region was considerable (Fig 4A). The squamous origin of this pavement epithelium in the subglottic region was demonstrated by both light microscopy and TEM (Fig 2B). It was difficult to assess accurately the proportions of squamous and respiratory epithelium covering the subglottic region, but by visual estimation the ratio varied from 1:3 to 1:1. The transition zone between the two epithelial types was also variable, not only in site (ie, distance from the free edge of the true vocal cord) but also in extent (ie, width of the zone where both cell types were present in appreciable numbers). In all cases, areas of squamous and respiratory epithelium were found in intimate association across the zone (Fig 4B), with TEM showing squamous cells interlinked by desmosomes and tonofibrils.

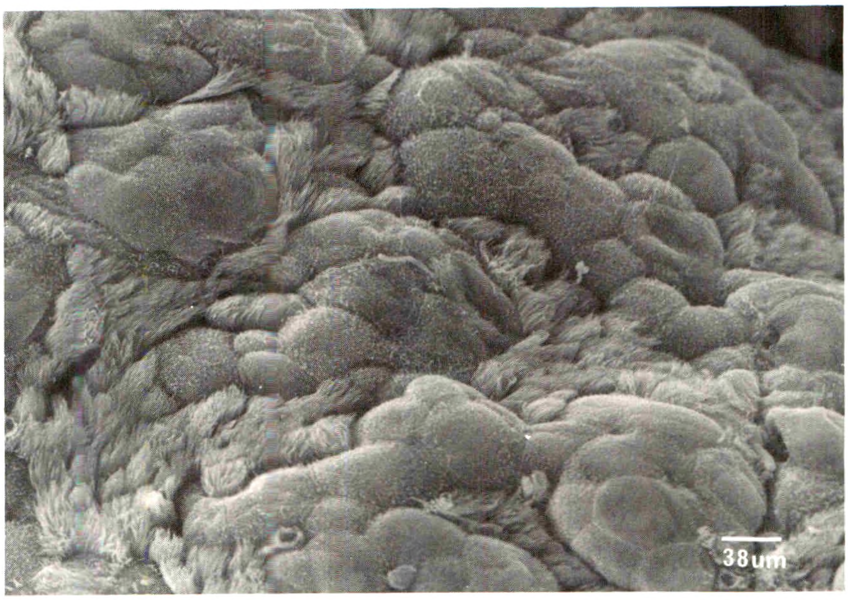

Fig 3. Scanning photomicrograph of free edge of epiglottis (original x730). Note areas of ciliated epithelium in close association with areas of epithelium with surface characteristics of squamous mucosa. Squamous origin of such areas was confirmed by subsequent TEM examination.

DISCUSSION

Using SEM and TEM, this study has provided further information about the distribution of the two types of epithelium in the human fetal larynx (Fig 1B). The ability to study the entire mucosal surface of the intact hemilarynx overcame problems of surface orientation that can occur with light microscopy techniques, while the identification of individual cells and cell types was achieved. The use of the OTOTO preparation technique enabled confirmation of the identity of cell types, as based on their characteristic surface appearance, by subsequent TEM examination of the same area of tissue. Carr and Toner[13] have suggested that SEM could play a major role in biomedical science, presenting structural information in a visual form that can be interpreted easily. Certainly, the results of this study show that the distinctive surface characteristics of the two epithelial types in the human larynx can be used alone to distinguish between them.

Previously, only macroscopic dye methods were used to study mucosal distribution over the intact surface of the larynx.[10] Although this is a quick and useful screening technique, small islands of cells of different types can be overlooked easily: an accurate assessment of epithelial distribution therefore cannot be made. Epithelial autolysis and surface mucus are two other factors that can lead to misinterpretation of the results of such studies. The material in this study was fixed within 40 minutes of the termination, resulting in good tissue preservation. Fortunately, surface mucus was conspicuously absent from all of the specimens.

Tourneux[1] first recorded that the true vocal cords were covered by squamous epithelium, and all subsequent studies have agreed with this observation. A squamous lining to the glottis has been noted as early as 14 weeks' gestational age.[2] The present findings support this observation, but the presence of ciliated cells scattered along the entire length of the true vocal cords in eight of the ten larynges studied was a previously unreported observation. The significance of these cells is conjectural: the few other light and electron microscopy studies of the adult human glottis have not reported them, and it can only be assumed that they are a transient feature of the growing larynx. Their presence, however, would suggest a close developmental association between the two types of epithelium lining both this and the other regions of the larynx. At the anterior commissure, the observation of a narrow vertical band of ciliated cells in two of the coronally sectioned larynges confirms a similar finding made in the adult larynx by Hilding.[14] Hilding also noted ciliated epithelium in the region of the posterior commissure, where dye studies[15] have shown only a broad vertical band of squamous epithelium. The present study showed this band to be flanked on either side by a narrower band of ciliated epithelium in all three suitably sectioned specimens. Whether the posterior commissure of the adult larynx would show the same features if studied by light and electron microscopy requires further study. Certainly, such a distribution of ciliated epithelium would provide a mechanism whereby mucus could be cleared across the posterior glottis.

In 1853 Rheiner[16] described the supraglottic region as having a ciliated columnar epithelial lining, except for the free edge of the epiglottis and aryepiglottic folds, where he found a squamous covering. Most subsequent work has supported Rheiner's findings, with minor differences in some cases. One notable exception was Rewell,[17] who found the posterior (laryngeal) surface of the epiglottis to be covered entirely by squamous epithelium. The findings of the present study do not concur with this observation. As Tucker et al[3] found in an electron microscopy study, the lingual surface of the epiglottis and

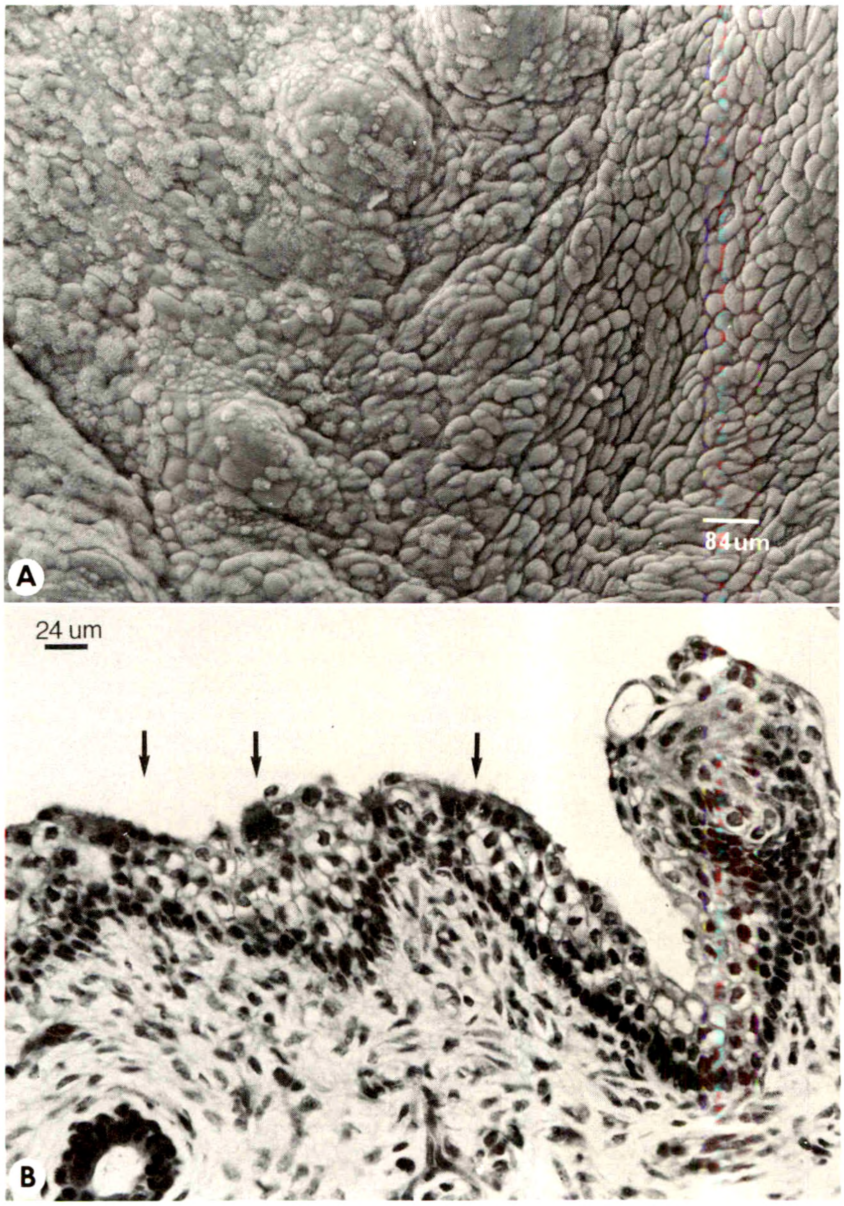

Fig 4. Photomicrographs of subglottic region of fetal larynges. A) Transition from squamous epithelium of upper subglottic region (to right of photomicrograph) to midportion of subglottic region, where ciliated cells are also present (original x260). Site and extent of transition zone varied from specimen to specimen. B) Light microscopic section of subglottic region shows stratified squamous type of epithelium with clusters of darker-staining ciliated respiratory cells in surface layer (arrows) (original x125).

the free edge of the laryngeal inlet were lined by squamous epithelium, which in the fetus was associated closely with respiratory epithelium over a broad zone. The rest of the supraglottic region was covered, almost entirely, by ciliated mucosa. Occasional islands of squamous cells were found scattered throughout the supraglottic regions of eight of the larynges examined in this study. These islands were seen more frequently on the laryngeal surface of the epiglottis than on the false vocal cords. Such findings have been documented previously only in adult studies. Using the alcian blue–phloxine staining technique, Stell et al[18] reported such islands in more than 50% of the larynges of nonsmoking adults. Hopp[2] considered that islands of squamous epithelium in the adult supraglottic region were rare and resulted from squamous metaplasia. The results reported here would disagree: such islands, although sometimes sparse in their distribution, were present in the majority of the supraglottic specimens studied. These two opposing schools of thought regarding such islands in areas of the larynx other than the glottis have existed for almost a century. The majority of opinion has argued that such areas are pathologic in nature. Kanthack[5] stated that they must be a result of pathologic metaplasia, as they could not be demonstrated in the fetal larynx. Stell et al[6] came to the same conclusion about their significance when they failed to find such islands in the subglottic region of neonates, even though they detected them, using surface dyes rather than microscopy, in this area of the larynx in 50% of larynges from nonsmoking adults. Until recently, only Heymann[4] believed that the islands were physiologic in origin; however, a recent study of the subglottic region of 34 pediatric larynges found areas of squamous epithelium in three of eight infants without a history of intubation.[9] Three of 11 stillborn infants and seven of 15 infants with a history of intubation also showed such areas. In the nonintubated subjects, the argument that the areas were due to squamous metaplasia consequent to trauma was invalid, and the possibility that subglottic squamous epithelium in neonates was congenital in origin was suggested by the authors. The present study would support this contention.

The epithelial distribution in the midtrimester fetal larynx is similar to that in the adult, both epithelial types often being found together in the nonglottic larynx. The concept of metaplasia would therefore seem inappropriate in the adult larynx when both types of epithelium are present in all areas from an early stage of development. Squamous metaplasia is usually the result of persistent trauma or chronic irritation,[19] factors alien to the normal fetal environment. Certainly, in view of the findings of this study, we feel that too much significance is placed on the observation of areas of so-called squamous metaplasia in the adult larynx. Only by the study of the relative proportions of the two types of epithelium throughout the development of the individual larynx can any definite conclusion be drawn as to whether or not squamous metaplasia has occurred.

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SYNAPTIC BODIES IN THE DIFFERENT ROWS OF OUTER HAIR CELLS IN THE GUINEA PIG COCHLEA

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The afferent synapses of the outer hair cells (OHCs) of the cochlea are peculiar, insofar as some of them contain special synaptic bodies (SBs) forming the so-called ribbon synapses. These SB-containing synapses are highly variable in number, exhibiting interspecies and intraspecies differences. As quantitative data on the incidence of SBs in the different rows of OHCs are lacking and as some of the above differences may have a circadian basis, in the present study SBs were counted in guinea pigs killed at different times of the day and night. In the second turn of the cochlea, synapses with perpendicular and parallel SBs were distinguished. Perpendicular SBs, but not parallel SBs, were significantly higher in number in the first than in the third row. Circadian changes were observed for perpendicular SBs, which were higher in number in the evening than in the morning. Circadian changes were absent in the parallel SBs of the OHCs and in the SBs of the inner hair cells. These results show that the afferent synapses of OHCs are rather complex, structurally as well as temporally; the functional significance of this finding remains to be elucidated.

KEY WORDS — cochlear hair cells, organ of Corti, synapses, synaptic bodies.

INTRODUCTION

In the membranous cochlea, the receptive hair cells include the inner hair cells (IHCs), forming a single row, and the outer hair cells (OHCs), arranged in three to five rows, depending on the species. The afferent synapses of IHCs and OHCs are characterized inter alia by the so-called synaptic bodies (SBs), which are variously shaped electron-dense organelles surrounded by electron-lucent synaptic vesicles. The electron-dense core has been thought to be involved in channeling synaptic vesicles to the presynaptic membrane in a conveyor-belt fashion (for review[1]) and/or to act as storage sites for neurotransmitters.[1,2]

A notable feature of the afferent synapses is that SBs are not always present. In IHCs of humans, SBs have been found in 83% of the afferent synapses, and in the OHCs, in only 35%.[3,4] In some species, OHCs even have been thought to lack SBs.[5-7] It is also noteworthy that the different rows of OHCs have various numbers of afferent synapses: in the second turn of the guinea pig cochlea, synapse numbers increase from the first to the third row,[8] but no quantitative data are available for the incidence of SBs in the different rows. Interesting new aspects of SBs become apparent when these structures are compared with similar organelles in other organs. In the pineal gland of guinea pigs, SBs exhibit a typical circadian rhythm, with small numbers during daytime and significantly higher numbers at night.[9] As a circadian rhythm also has been noted for SBs of retinal photoreceptor cells,[10,11] the possibility exists that the reported lack of SBs in OHCs is due to rhythmic changes. Hence, it appeared worthwhile to obtain data on numbers of SBs in animals killed at different times of the day and night.

MATERIALS AND METHODS

In the present study, we used 29 male Pirbright White guinea pigs, with body weights ranging from 512 to 1,295 g. They had been used in an experiment in which all the animals walked on a moving conveyor belt (speed, 2.75 m/min) for 2 hours each day (9 to 10 AM and 2 to 3 PM) for 3 weeks, except the last day before killing. They had been kept in Scanbur guinea pig cages, five per cage, under routine laboratory conditions (LD 12:12, lights on at 6 AM, fluorescent strip lights, 300 lux at the bottom of the cages, temperature 21°C, 50% to 60% humidity; free access to water and guinea pig chow, Altromin). The animals were anesthetized (after blindfolding with black Scotch tape at night) with Nembutal (30 mg/kg body weight, given intraperitoneally) and killed by perfusion-fixation via the left cardiac ventricle with the fixative of Ito and Karnovsky[12] (room temperature) at 4 AM, 8 AM, and 12 noon (Feb 20, 1984); 4 PM (Feb 7, 1984); and 8 PM and 12 midnight (Feb 14, 1984), respectively. After decapitation, the dissection of the cochlea (in 26 cases, the right cochlea; in the case of a diseased right cochlea, the left one) was carried out according to the method of Smith and Vernon.[13] A hole was drilled in the apex of the cochlea, the round and oval windows were opened, and fixative solution (5% phosphate-buffered glutaraldehyde, pH 7.3) was infused through the apical hole for 5 minutes. Then the whole cochlea was immersed in identical fixative for 4 hours, followed by immersion in the fixative of Ito and Karnovsky[12] for 12 hours with gentle shaking. Subsequently, the tissue was rinsed in sodium cacodylate buffer (0.1 *M*, pH 7.3), postfixed in 4% buffered osmium tetroxide for 3 hours, then rinsed in sodium cacodylate buffer as before,

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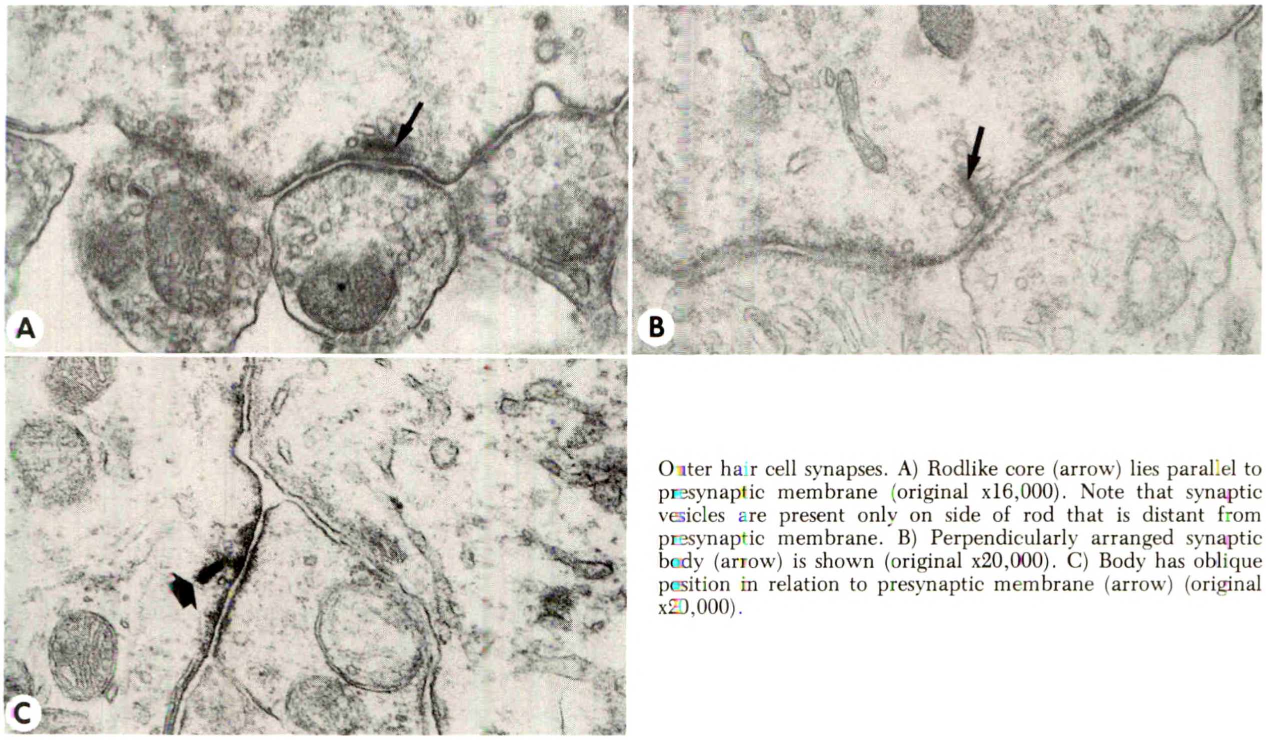

Outer hair cell synapses. A) Rodlike core (arrow) lies parallel to presynaptic membrane (original x16,000). Note that synaptic vesicles are present only on side of rod that is distant from presynaptic membrane. B) Perpendicularly arranged synaptic body (arrow) is shown (original x20,000). C) Body has oblique position in relation to presynaptic membrane (arrow) (original x20,000).

followed by dehydration in graded series of ethanol. At the 70% ethanol stage, the tissue was stained en bloc with 5% uranyl acetate for 60 minutes. The tissue was embedded in Epon, and after hardening of the resin, the cochlea was cut in half along the modiolus, followed by a dissection of the second turn, which then was cut in half and reembedded in Epon in such a way that the hair cells could be sectioned longitudinally. Semithin sections were cut for light microscopy, and thin sections for electron microscopy. Before thin sectioning, most of the bone present had been removed. Thin sections were stained in 8% aqueous uranyl acetate for 10 minutes, followed by 10 minutes of lead-citrate staining.[14]

For the qualitative and quantitative evaluation of the SBs, 100 step-serial sections were cut through the neural poles of the hair cells, ie, ten serial sections from ten different levels 5 μm apart. To gain insight into the three-dimensional structure of the SBs, but to ease the counting procedure (profiles of serially sectioned SBs are to be counted as one SB only), only the first three and the last three sections of a series were used, discarding the four central ones. Hence, for each animal, 60 sections from each cell row were evaluated. In a number of groups, the long and short diameters of SBs were measured by means of a Morphomat 10 (Kontron) attached to a Zeiss 109 electron microscope, at a magnification of x50,000.

To test whether differences existed between the different rows of hair cells, the Friedman's test was used and was followed, when appropriate, by the Wilcoxon and Wilcox test. The Kruskal-Wallis H-test was applied to test for differences related to time. As in one group the number of observations was smaller than in the others, the Kruskal-Wallis test could not be followed by the Nemenyi test to find out between which times significant differences existed. Hence, the Wilcoxon-Mann-Whitney U-test was applied to compare those times that differed most according to the rank sums of the Kruskal-Wallis test. Further, Spearman's coefficient of rank correlation was computed. For tabulating the data and for the sake of convenience, the means plus/minus the standard errors of the means also were calculated.

RESULTS

In the present study, 450 profiles of ribbon synapses in OHCs and 396 such profiles in IHCs were evaluated, including some profiles in which SBs lay clearly distant from the cell membrane. The term synaptic profile instead of synapse is used, as the synapses extend over several sections and hence cannot be studied in toto.

General Appearance of Afferent Synapses. The general structure of the afferent ribbon synapses of the OHCs and IHCs seen in this study conformed to that described by other authors (see Introduction). The synapses often were characterized by thickening of the presynaptic and postsynaptic membranes, and close to their active zones the presynaptic membrane frequently exhibited coated pits. The majority of the synaptic profiles showed a single SB. In the OHCs, 20.9% of the profiles contained two or three SBs; in the IHCs, only 4% exhibited two SBs. The form of the SBs differed between OHCs and IHCs.

NUMBER OF SYNAPTIC BODIES IN HAIR CELLS AS FUNCTION OF TIME

Time of Killing	*Inner Hair Cells*	*First Row Outer Hair Cells*		
		Total	*Perpendicular*	*Parallel*
4 AM[a]	11.75 ± 0.63	6.0 ± 1.68	2.25 ± 1.03	2.75 ± 1.03
8 AM[a]	13.20 ± 2.01	3.2 ± 1.43	0.60 ± 0.40[j]	2.40 ± 1.16
12 Noon[a]	10.80 ± 2.69	4.2 ± 1.28	2.20 ± 0.49[k]	1.20 ± 0.49
4 PM[b]	13.00 ± 0.71	7.2 ± 1.43	3.80 ± 0.97[l]	2.40 ± 0.51
8 PM[c]	16.80 ± 2.63	8.2 ± 1.02	4.20 ± 0.80[m]	2.80 ± 0.73
12 Midnight[c]	16.00 ± 2.72	6.6 ± 0.68	5.40 ± 0.68[n]	0.80 ± 0.37
Mean	13.59 ± 1.90[d]	5.9 ± 1.25[e]	3.08 ± 0.73[f]	2.06 ± 0.72
	NS[o]	NS	$p < .025$	NS

In outer hair cells, synaptic bodies have been subdivided according to their location with respect to presynaptic membrane, ie, perpendicular and parallel arrangement. In total number of SBs, some obliquely arranged SBs are included, as are some SBs lying distant from presynaptic membrane. Mean ± standard error of mean per 60 profiles of neural poles of hair cells.

[a-c] Only animals with identical letters were killed within one 24-hour period (for details, see Materials and Methods).

[d-n] For *d* vs *e,g,h*: $p < .01$; *f* vs *i*: $p < .05$; *j* vs *k,l*: $p < .05$; *j* vs *m,n*: $p < .01$; NS: $p > .05$.

[o] Statistical evaluation given in this row relates to temporal changes. There were no time-related differences when data from all OHCs were pooled.

In the OHC, SBs invariably appeared as elongated, rodlike structures measuring between 100 and 450 nm in length and approximately 40 nm in width (see Figure), which, as seen in serial sections, represent sections through platelike structures. The position of the rod varied in relation to the presynaptic membrane. Five percent of the SBs lay clearly distant from it. The remainder were found parallel (44%; Figure, A), perpendicular (42.4%, Figure, B), or oblique (8.6%; Figure, C) to the presynaptic membrane. Often, electron-dense material triangular in shape and measuring 30 to 40 nm in height was seen between the SBs and the presynaptic membrane, sometimes giving the impression that it was linking the two structures. In the case of parallel-lying SBs, usually two of these triangular bodies were seen. The electron-lucent vesicles surrounding the electron-dense rod varied from round to oval or flattened. They formed a single layer, individual vesicles often being attached to the rod by delicate stalks. The number of vesicles per rod varied considerably.[15] Those SBs that were parallel to the presynaptic membrane lacked vesicles on the side of the rod facing the presynaptic membrane.

The profiles of SBs in the IHCs were highly pleomorphic. Their central cores appeared club-shaped, bar-shaped with differing widths and lengths, or rod-shaped similar to the SBs of the OHCs, though distinctly longer (up to 870 nm). The dimensions of the club-shaped SB profiles ranged from 120 to 200 by 100 to 150 nm, whereas those of the bar-shaped organelles ranged from 230 to 400 by 80 to 150 nm. Both of these structures were 1) homogeneously dense, 2) laminated, or 3) electron-lucent in the center, the peripheral wall being either homogeneously dense or laminated. The width of the electron-dense wall measured 30 to 40 nm. Serial sections revealed that the organelles with an electron-lucent center were cylinderlike structures with both ends closed.

Quantitative Data. The Table shows that when the data obtained at the different times are jointly considered, SBs in the IHCs are approximately three times as numerous as in each of the three rows of OHCs ($p < .01$, Wilcoxon and Wilcox test). The numbers of SBs in the different rows of OHCs do not differ. When perpendicular and parallel SBs of the OHCs are evaluated separately, however, the perpendicular SBs are significantly higher in number in row 1 than row 3 ($p < .05$, Wilcoxon and Wilcox test). The numbers of parallel SBs do not differ between rows. There is no relationship between the numbers of perpendicular and parallel SBs in the different rows, neither when all the animals are considered jointly nor when the animals prepared at a given time are analyzed (Spearman's rank correlation coefficient).

With respect to time of day, the only significant differences noted were among the perpendicular SBs of the first row of OHCs (OHC1) ($p < .025$, Kruskal-Wallis test). In this row, the data at the individual times reveal a sinusoidal curve with a trough at 8 AM and a peak at midnight, the other values being intermediate. The Wilcoxon-Mann-Whitney U-test shows that the 8 AM value differs significantly from the noon ($p < .05$), 4 PM ($p = .05$), 8 PM ($p < .01$), and midnight ($p < .01$) values.

DISCUSSION

Different opinions exist about the presence or absence of SBs in OHCs of the membranous cochlea (see Introduction). Most studies using guinea pigs found SBs,[8,16,17] but Pujol et al[7] stated categorically that SBs are absent. We feel that the reported lack of SBs in guinea pig OHCs may be attributed to the fact that SBs are relatively rare. In our material, between 0 and 13 SBs per 60 OHC profiles have been observed, indicating that large numbers of sections have to be scanned before reliable data can be obtained.

An interesting new finding is that the elongated SBs of the OHCs show a variable arrangement with respect to the presynaptic membrane. In previous studies, it was seen that SBs typically lie perpendicular to the presynaptic membrane,[8,16] although sometimes parallel-lying SBs have been encountered.[16] The results of this study show that in 450

NUMBER OF SYNAPTIC BODIES IN HAIR CELLS AS FUNCTION OF TIME (continued)

Time of Killing	*Second Row Outer Hair Cells*			*Third Row Outer Hair Cells*		
	Total	*Perpendicular*	*Parallel*	*Total*	*Perpendicular*	*Parallel*
4 AM[a]	4.25 ± 1.33	1.50 ± 0.29	2.75 ± 1.55	5.00 ± 1.22	1.05 ± 0.50	2.75 ± 0.75
8 AM[a]	5.00 ± 1.45	2.20 ± 0.58	2.20 ± 0.66	2.20 ± 0.66	1.00 ± 0.45	1.20 ± 0.73
12 Noon[a]	4.00 ± 1.14	1.40 ± 0.75	1.80 ± 0.80	5.00 ± 1.05	1.20 ± 0.73	3.00 ± 0.89
4 PM[b]	7.80 ± 1.39	3.20 ± 1.00	3.40 ± 1.21	3.80 ± 0.80	1.60 ± 0.51	1.80 ± 0.58
8 PM[c]	5.20 ± 0.86	2.20 ± 0.37	2.00 ± 0.84	3.80 ± 0.73	1.40 ± 0.75	1.60 ± 0.24
12 Midnight[c]	6.80 ± 1.39	2.80 ± 0.58	3.00 ± 0.71	5.00 ± 0.84	1.40 ± 0.75	3.20 ± 0.86
Mean	5.51 ± 1.26[g]	2.22 ± 0.61	2.53 ± 0.96	4.13 ± 0.88[h]	1.35 ± 0.62[i]	2.26 ± 0.68
	NS	NS	NS	NS	NS	NS

SBs analyzed, perpendicular and parallel structures were equally abundant. The significance of the different arrangements of the synaptic organelles is not clear. Perhaps this phenomenon has functional significance. A current hypothesis is that the electron-dense core of the SB channels the surrounding electron-lucent synaptic vesicles to distinct sites of the presynaptic membrane (conveyor-belt hypothesis).[1] As perpendicular SBs have synaptic vesicles on both sides, but parallel SBs lack vesicles on the side facing the presynaptic membrane, perpendicular SBs appear to be better suited for channeling synaptic vesicles to the presynaptic membrane than parallel-lying SBs. We therefore speculate that synapses with parallel-lying SBs are functionally less active than synapses with perpendicular SBs. The possibility exists that the perpendicular and parallel SBs are expressions of positional changes, depending on the functional state of the synapse. Should perpendicular SBs move to a parallel location, and vice versa, the numbers of the two types should be negatively correlated. As this was not the case, the hypothesis that SBs change position is not likely. Assuming that synapses with parallel SBs are less active than those with perpendicular ones, then the high incidence of parallel SBs could be viewed similarly to the postnatal decrease of SBs in the OHCs,[18] which would abate the influence of SBs on synaptic transmission.

Another new aspect of OHCs is that the perpendicular SBs decrease in number from the first to the third row. Since the number of afferent synapses increases in this direction,[8] it follows either that in the third row of OHCs (OHC3) an individual afferent synapse has fewer SBs, or that there are more afferent synapses without SBs. The presence of a varying number of SBs per synapse and a change in the number of SBs per synapse has been well documented in the developing organ of Corti in mice.[18] A structural heterogeneity of the synapses in the different rows of OHCs also has been described with respect to reciprocal synapses, which are more abundant in the third than in the first row.[19] Whether these structural differences have consequences with respect to function remains to be established. That this may be the case is suggested by the finding that the number of highly active nuclei is highest in the first row,[20] and that the order of damage to OHCs after exposure to loud sounds is OHC1 > OHC2 > OHC3.[21]

Finally, there is evidence from the pineal gland and retina that SBs exhibit 24-hour changes in number.[9-11] The results obtained in this study suggest that the concept of 24-hour rhythmicity of SB numbers also may apply to the organ of Corti, specifically to the afferent synapses with perpendicular SBs in OHC1. As the animals studied were not killed throughout a single 24-hour cycle, the results cannot be regarded as definitive; however, it appears that in the same material one row of hair cells does show time-related changes in the number of SBs, whereas others do not. The reason for this difference is not clear. In the case of the pineal gland, efferent sympathetic nerve fibers are responsible for circadian changes in melatonin synthesis.[22] Since in the organ of Corti the efferent innervation is particularly pronounced in OHC1,[8,23] it is tempting to conclude that this differing innervation density accounts for the temporal differences observed in this row.

In conclusion, this study has shown that the problem of the afferent innervation and the function of the different rows of OHCs cannot be assessed properly unless the number, arrangement, and temporal patterns of the SBs are taken into consideration.

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ULTRASTRUCTURE OF MUCOUS BLANKET IN OTITIS MEDIA WITH EFFUSION

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We used transmission electron microscopy to study the mucous blanket of the promontory from children with otitis media with effusion. The vast majority of the epithelial cells were secretory, and the rest were ciliated. The mucous blanket consisted of the electron-lucent periciliary fluid and the mucous layer. In the mucous layer, two layers were identified: an inner layer with migrating cells, and an outer layer with specks. Moreover, there was a lucent zone over the nonciliated surface that was as high as the microvilli. The thickness of the periciliary layer was predominantly as great as that of the ciliary tips, which just make contact with the mucous layer; however, the mucous layer occasionally penetrated into the periciliary space. These findings indicated that there is a mucociliary dysfunction in the middle ear caused by a decrease in the number of ciliated cells, and an abnormal interaction between cilia and mucus that would interfere with ciliary movement. Thus, such a system would fail to transport the mucous blanket.

KEY WORDS — cilia, microvilli, middle ear effusion, mucociliary clearance, mucous blanket, mucus, otitis media with effusion, periciliary fluid.

Middle ear effusion (MEE) of chronic otitis media with effusion (OME) is believed to be a locally produced inflammatory product composed of plasma components, inflammatory cells, and secretions. Although the pathogenesis of this disease is not fully understood, it can be asserted that as a result of the disease, effusion accumulates in the middle ear cavity. Thus, the disease may be defined simply as the middle ear cavity's inability to eliminate the retained effusion. It has been accepted that elimination of the fluid from the middle ear takes place by two separate mechanisms: 1) the pumping action of the eustachian tube[1] and 2) mucociliary transport of the middle ear and the eustachian tube.[2,3] Therefore, dysfunction of mucociliary transport in the tubotympanic system could be a cause of the accumulation of fluid in the middle ear.[4,5]

Mucociliary transport is a function of the interaction between cilia and mucus.[6-9] Sufficient density and normal beat frequency, amplitude, and coordination of cilia are required for efficient ciliary activity. The rheologic properties of mucus have a relatively narrow range for effective mucociliary clearance.[10] In view of the bilayered structure of the mucous blanket[11,12] (the mucous layer and the periciliary fluid), the depth of the periciliary fluid is critical for the interaction of cilia and mucus.[13] If it is too deep, the tips of the cilia will not catch the mucous layer on their effective strokes; if it is too shallow, the cilia will not be able to beat actively.

It is very difficult, however, to retain the mucous blanket in situ for electron microscopic observation of the interaction of cilia and mucus. In this study, we observed the mucous blanket of the middle ear from children with OME, taking the greatest care to preserve the mucous blanket in situ. Special attention has been paid to the relationship between the luminal surface of the epithelium and the mucous blanket.

MATERIALS AND METHODS

We used mucosal biopsy specimens from eight children 5 to 9 years of age with OME. The diagnosis was made by clinical symptoms, pure tone audiometry, and impedance measurement. At myringotomy, all patients had a mucoid fluid in the middle ear. After myringotomy, under general anesthesia, a biopsy specimen was taken from the promontory with small ear forceps. The procedure was completed by the removal of MEE by aspiration and the insertion of a ventilation tube.

The specimen was fixed immediately in cold 2.5% glutaraldehyde for 2 hours without any vibration and, without washing, glutaraldehyde postfixed in cold buffered 1% osmium tetroxide for 1 hour. After stepwise dehydration, the specimens were passed through propylene oxide and embedded in Quetol 812 (Nissin EM, Tokyo).

For light microscopy, 1- to 2-μm sections were stained with 1% toluidine blue. Thin sections were stained with uranyl acetate and lead citrate and studied under a JEM 100B electron microscope.

RESULTS

The following study was based on observations from six of eight cases; in two cases, the mucous blanket was not preserved completely.

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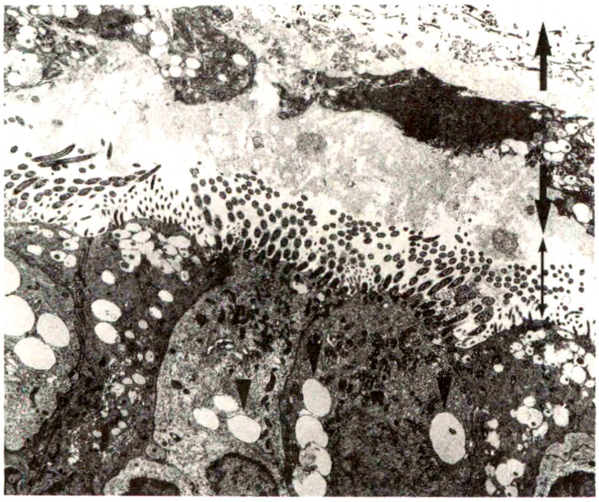

Fig 1. Mucous blanket consisting of periciliary fluid (small arrows) and mucous layer (large arrows) (original x6,000). Mucous layer is sitting at tips of cilia. Layer between lower edge of mucous layer and luminal surface of epithelium is electron-lucent (periciliary fluid layer). Ciliated cell contains numerous large secretory granules (arrowheads) around nucleus.

In the promontory of OME, four main types of cells were observed: ciliated cells, nonciliated cells, goblet cells, and basal cells. The thickness of the epithelium varied considerably. There were tall columnar pseudostratified epithelia and one- or two-layered cuboidal epithelia. The expansion of the intercellular space was not observed.

The blood vessels were dilated in the edematous lamina propria. Inflammatory cells in the lamina propria were neutrophils, lymphocytes, plasma cells, and macrophages. Although no glandular tissue was found, there were some rudimentary glands from the lining epithelium, as described by Tos and Bak-Pedersen.[14]

Only two cell types were identified on the luminal surface of the promontory in OME; the vast majority of them were secretory cells, and a few were ciliated cells. The few ciliated cells present contained numerous large membrane-bound secretory granules around the nucleus. These granules were electron-lucent and occasionally contained a small spiral structure. In the mucous blanket, these granules were not found. Although some compound cilia were observed, there was no abnormality in the microtubular arrangement of cilia.

Mixed granulated cells that contained prominent endoplasmic reticulum and light secretory granules with high density cores were overwhelmingly predominant in the secretory cell population over high density secretory cells with dark vesicles.

As shown in Fig 1, the mucous blanket consisted of the periciliary fluid and the mucous layer. The depth of the periciliary layer that constituted the electron-lucent zone around the cilia was a little less than the length of the cilia. In the nonciliated area, there was also a lucent layer over nonciliated cells with a depth as great as that of the microvilli (Fig 2). The depth of the lucent layer on the nonciliated cells in the ciliated area was as great as on the neighboring ciliated cells (Fig 3).

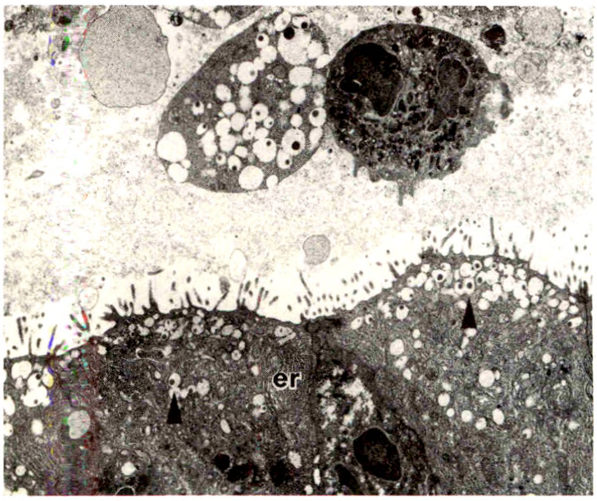

Fig 2. Electron-lucent zone over nonciliated surface of epithelium (original x8,000). Goblet cell contains prominent endoplasmic reticulum (er) and light granules with high density core (arrowheads). Neutrophil and secretory granule can be seen in mucous layer.

Large individual variations occurred in the thickness of the mucous layer, which was clearly made up of two layers (Fig 4A). Numerous specks floated in the luminal layer. Many fragments of cell organelles were seen between the fibrous stands of varying sizes (Fig 4B,C). The surface of the layer was relatively smooth. The inner layer contained migrating cells, cellular debris of desquamated epithelial cells, and discharged granules from goblet cells with a fine homogeneous texture (Fig 4A). Migrating cells were mainly neutrophils and macrophages.

Where the secretory activity was high in the goblet cells, cilia were pressed by released secretory

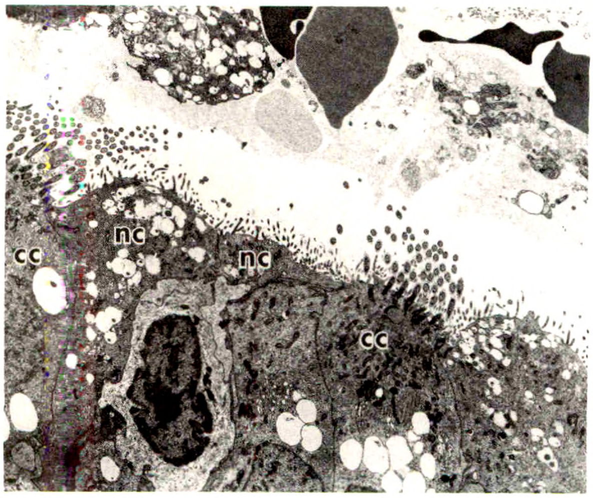

Fig 3. Lucent zone over two nonciliated cells (nc) (original x6,000). Depth is same as over adjacent ciliated cells (cc).

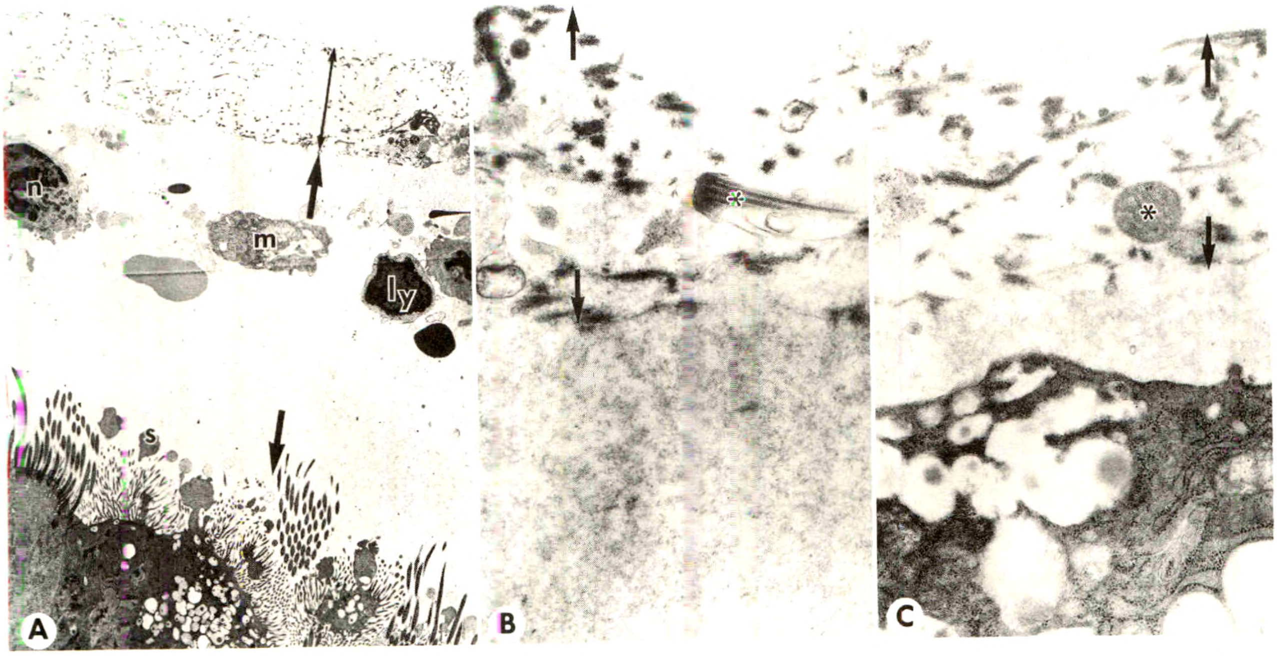

Fig 4. Two layers identified in mucous layer. A) Luminal layer with specks (small arrows) and inner layer with migrating cells (original x4,700). Macrophages (m), neutrophils (n), lymphocytes (ly), and various secretory granules (s) are seen in inner layer (large arrows) of mucous layer. B) In luminal layer of mucous layer (arrows), fragments of cilium (asterisk) are seen between fibrous strands of various sizes (original x40,000). C) Swollen mitochondria (asterisk) in luminal layer (arrows) (original x40,000).

granules (Fig 5). In these areas, the rows of cilia were buried so deeply in the mucous layer that the periciliary fluid layer was lowered (Fig 6), suggesting that there was an abnormal interaction between cilia and mucus. The relationship between the luminal surface and the mucous blanket is presented schematically in Fig 7.

DISCUSSION

Two mechanisms are involved in the elimination of mucus from the middle ear cavity toward the nasopharynx: 1) mucociliary clearance and 2) muscular clearance of the eustachian tube. Both clearances may be mutually complementary in the normal situation; however, these different evacuation systems essentially cannot compensate for each other. With ciliary dysfunction in primary ciliary dyskinesia (Kartagener's syndrome),[15] OME develops in spite of normal tubal muscular clearance; and with muscular dysfunction caused by a cleft palate,[16] OME develops in spite of normal mucociliary clearance. Therefore, the importance of the mucociliary transport function has been recognized widely. In 1967, Sadé[2] pointed out that mucous clearance of the middle ear is an active process that is related to its ciliary function.

Although extensive studies have been devoted to the ultrastructure of the mucociliary apparatus, the mucous blanket has not been studied sufficiently. The reason for this is that adequate preservation of the mucous blanket is technically difficult.[17,18]

In 1976, using a fixative vapor and a transmission electron microscope, Yoneda[19] observed the ultrastructure of the mucous blanket of the normal rat bronchus. In 1978, using a fixative of stabilizing carbohydrate and a transmission electron microscope, Reissig et al[20] studied the ultrastructure of the mucociliary interface of normal chicken nasal mucosa. Recently, Takasaka and Kawamoto[21] investigated the morphologic change in the mucociliary transport system in experimental OME in guinea pigs and chinchillas.

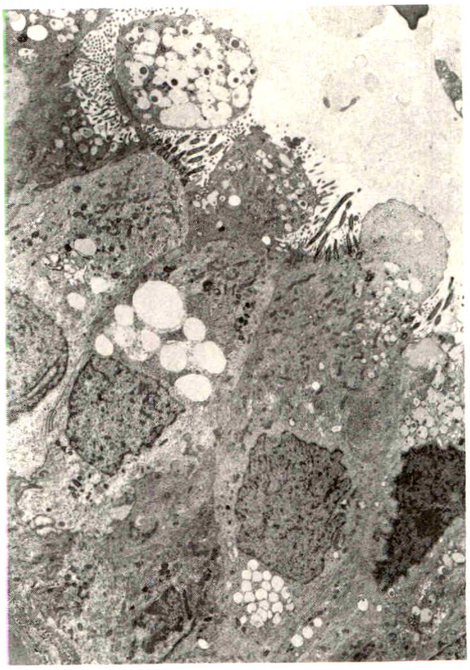

Fig 5. In place where secretory activity is high in goblet cells, cilia are pressed by adjacent goblet cells (original x6,000).

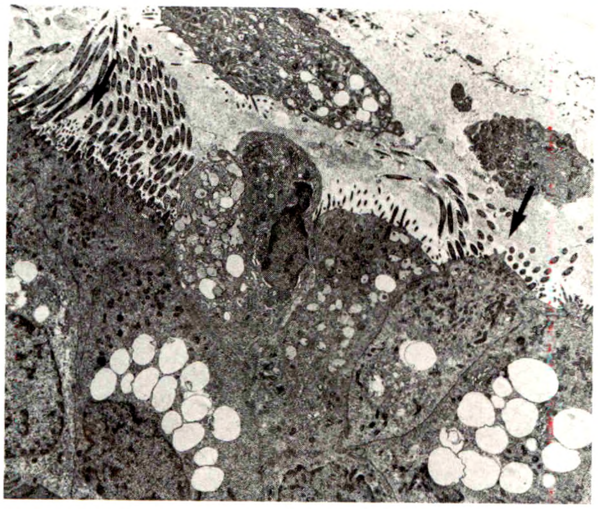

Fig 6. Mucous layer deeply penetrating into periciliary space (arrows), suggesting abnormal interaction between cilia and mucus (original x6,000).

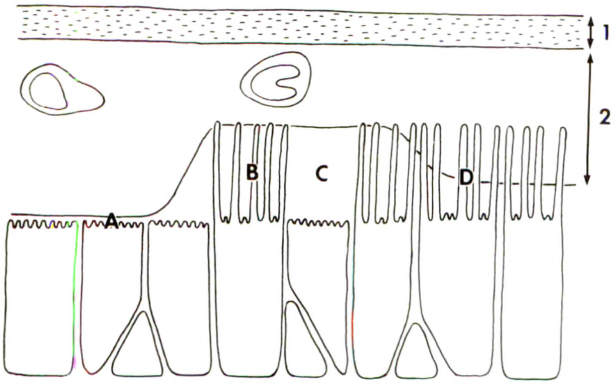

Fig 7. Schematic representation of mucous blanket, showing thin electron-lucent layer (A) on nonciliated cells with microvilli, periciliary fluid layer (B) in normal situation, thick lucent layer (C) on nonciliated cells with microvilli surrounded by ciliated cells, and shallow periciliary fluid layer (D) in presence of disease. Mucous layer consists of two layers: luminal layer (1) with numerous specks, and inner layer (2) with migrating and desquamated cells and secretory granules.

We have identified the ultrastructure of the mucous blanket of human middle ear in OME. As we used small samples of tissue, avoided making any impact on the samples, and tried to keep the samples undisturbed during fixation, we obtained good preservation of the mucous blanket with conventional glutaraldehyde-osmium fixative.

The present study confirmed a double-structure concept of the mucous blanket. Over most of the ciliated surface, the mucous layer was sitting at the tips of the cilia, and the layer between the lower edge of the mucous layer and the luminal surface of the epithelium was electron-lucent where the ciliary shafts were immersed. On the rest of the ciliated surface, the mucous layer penetrated deeply into the periciliary space. It is obvious that adequate ciliary beat frequency and amplitude are not enough for efficient mucociliary transport to take place. This finding is the same as that observed in the promontorial mucosa of patients with OME,[22] and in OME induced in animals experimentally.[21]

Penetration of the mucous layer into the periciliary space could be caused by an increase in amount and/or change in biochemical composition of the mucus; mucosubstances in normal mucus may prevent its settling into the periciliary space.[23] On the other hand, it may be due to a decrease in periciliary fluid from an unknown cause, or a combination of both.

One of the prevailing hypotheses of periciliary fluid regulation has been that it results from the function of microvilli-equipped cells, ciliated and nonciliated.[24,25] An electron-lucent layer existed around the ciliary shafts on the luminal surface of the ciliated area; at the same time, a lucent layer existed on the surface of the nonciliated area. The lucent layer on the ciliated surface, however, was thicker than that on the nonciliated surface. This fact suggests that both types of microvilli-equipped cells could control periciliary fluid. The difference in the thickness of the fluid between both surfaces may indicate that the microvilli of the ciliated cells play a more important role in regulating periciliary fluid. Another possibility that cannot be abandoned, however, is that the fluid could result from a liquefying effect of cilia beating on mucus—thixotropy.[24]

Tos[26] stated that under abnormal conditions the flat nonciliated epithelium of the middle ear was transformed into pseudostratified ciliary epithelium with an increase in goblet cells.

Møller and Dalen[27] reported that the mucosa mainly consisted of secretory cells and that ciliated cells occupied about 5% of the promontory surface in OME. Although the present study was not quantitative, it does support these findings. It was found that the vast majority of the surface of the epithelium was composed of secretory cells and that the rest were ciliated. Intense hyperplasia of the goblet cells caused the relative decrease in the number of ciliated cells. The ciliated cells were too scarce for abundant mucus to be transported. Moreover, the lowered mucous layer disturbed ciliary activity; ciliary beating was reduced or ceased, and its amplitude would not be complete in sticky mucus. It has been reported that there is mucociliary dysfunction in otitis media.[4,5] These results indicate that there is mucociliary dysfunction in the middle ear in OME caused by lack of cilia and abnormal interaction of cilia and mucus. This dysfunction could be a cause of mucus accumulation in the middle ear cavity in this disease.

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COLLAGEN COMPONENTS OF BOVINE FETAL AND GUINEA PIG COCHLEAR BONE AND HUMAN STAPES

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Collagenous components were isolated chemically from fetal bovine or guinea pig cochlear bone and human stapes after stapedectomy, and the purified protein was characterized by immunoblot assay and amino acid analysis. The results of this study suggest that these are mixtures of type I and type II collagens. The presence of type II collagen in the human stapes also was demonstrated by immunohistologic methods using monoclonal antibody. The presence of type II collagen in these tissues is significant, since it has been postulated as an autoantigen in autoimmune inner ear disease.

KEY WORDS — cochlear bone, collagens, Meniere's disease, otosclerosis, stapes.

INTRODUCTION

The causes of otosclerosis and Meniere's disease are obscure.[1-4] We recently described autoimmune hearing loss, vestibular dysfunction, and otospongiotic lesions in rats.[5-7] A similar inner ear disease can be induced experimentally in guinea pigs by immunization with type II collagen.[8] Since these abnormalities appeared to be associated with autoimmunity against type II collagen,[9] it was therefore of interest to examine the collagenous structures of the cochlea and auditory ossicles.

METHODS AND MATERIALS

Preparation of Cochlear Bone and Stapes. The cochlear bones were removed from fetal calves obtained from a local slaughterhouse, or from guinea pigs obtained from the Office of Mammalian Genetics and Animal Production Section, National Cancer Institute (Frederick Cancer Research Center, Frederick, Md). The human stapedes were obtained following stapedectomy (donated by Otology Clinic, Beziers, France), cleaned of adherent tissue, and pulverized in liquid nitrogen. The bone powder was suspended in 0.35 *M* EDTA, pH 8.1, in 0.2 *M* Tris-HCl and was decalcified at 4°C with several changes of buffer. The decalcified powder was washed with water several times and finally washed with 0.5 *M* acetic acid, followed by centrifugation. The insoluble pellet was suspended in 0.5 *M* acetic acid and was digested with pepsin (enzyme-substrate ratio, 1 to 100 wet weight). After 48 hours, the pepsin digest was centrifuged and pepsin was deactivated in the supernatant by the addition of 1.0 *M* NaOH, pH 8.0. The collagen was precipitated by the addition of 20% solid NaCl. The collagen precipitate was collected by centrifugation, and the pellet was redissolved in 0.05 *M* Tris-HCl/0.2 *M* NaCl, pH 7.2. The collagen solution was dialyzed against 0.5 *M* Tris-HCl/0.2 *M* NaCl, pH 7.2, and was applied to a DEAE-cellulose column prepared in the same buffer. The unbound effluent peak was collected and dialyzed against 0.02 *M* acetate/2 *M* urea, pH 4.8. The final purification was performed on a carboxymethyl cellulose column at 15°C prepared in 0.02 *M* acetate/2 *M* urea, pH 4.8. The column was eluted with a linear salt gradient consisting of 0 to 0.12 *M* NaCl in 0.02 *M* acetate/2 *M* urea, pH 4.8, and a single homogeneous peak was obtained. The purified collagen was analyzed for amino acid composition and by polyacrylamide gel electrophoresis.

Immunoblot Assay. Samples were analyzed with 5% NaDodSO4 polyacrylamide gel electrophoreses (NaDodSO4-PAGE) according to the method used by Lammeli.[10] The gel was transblotted onto nitrocellulose paper with 0.025 *M* Tris-HCl, pH 8.3/0.192 *M* glycine and 20% methanol for 6 hours with a constant current of 250 mA. The nitrocellulose paper was transferred to 0.02 *M* Tris/0.5 *M* NaCl, pH 7.5 (TBS) containing 3% (vol/vol) for 3 hours. After five washes with TBS, the nitrocellulose paper then was transferred to a 1/1,000 dilution of monoclonal anti-type II collagen antibody containing 1% horse serum. After incubation overnight in the cold room, the nitrocellulose paper was washed five times with TBS and transferred to a so-

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AMINO ACID COMPOSITION OF BOVINE COCHLEA AND HUMAN STAPES (RESIDUES PER 1,000 AMINO ACIDS)

	Bovine Cochlear Bone	*Human Stapes*	*Human Type I* $\alpha 1(I)$[14]	*Human Type I* $\alpha 2(I)$	*Human Type II* $\alpha 1(II)$[15]
4-Hydroxyproline	97	93	96	82	99
Aspartic acid	45	39	41	47	42
Threonine	18	15	16	19	20
Serine	28	30	37	35	26
Glutamine	76	85	71	68	90
Proline	118	110	133	120	121
Glycine	330	336	336	337	332
Alanine	130	126	115	105	100
Valine	18	16	20	33	18
Methionine	7	8	7	5	9
Isoleucine	10	12	7	15	9
Leucine	18	24	20	30	25
Tyrosine	2	2	2	1	1
Phenylalanine	14	15	12	12	13
Hydroxylysine	12	11	5	8	14
Lysine	28	26	30	22	22
Histidine	2	2	2	10	2
Arginine	53	51	49	51	51

lution of TBS containing goat anti-mouse horseradish peroxidase (HRP) conjugate (1/2,000 dilution) for 3 hours at room temperature, with shaking. At the end of this incubation, the nitrocellulose paper was washed five times with TBS and transferred to the developing solution, which contained 60 mg HRP color development reagent in 30 mL of cold methanol and 60 μL of ice cold H_2O_2 (30%) in a total volume of 120 mL. A purple color appeared within 10 minutes,[11,12] indicating the presence of type II collagen. Monoclonal antibody against type II collagen[13] was donated by the VA Medical Center, Memphis.

Histology. The stapedes were fixed in 95% cold ethanol and decalcified with 5% EDTA and embedded in 56°C melted paraffin. Sections were deparaffinized and treated with hyaluronidase to extract proteoglycans that mask antigenic sites of type II collagen.

RESULTS AND DISCUSSION

From these preliminary results, stapedial and cochlear bone appear to contain predominantly type I collagen. The amino acid composition of the stapedial and cochlear bone is shown in the Table. The amino acid contents suggest they contain predominantly collagen. For comparison, the amino acid composition of human type I $\alpha 1(I)$, type I $\alpha 2(I)$, and type II $\alpha 1(II)$ collagens are presented.[14,15] The significant differences are the number of hydroxylysine residues per 1,000 amino acids. The higher content of hydroxylysine is suggestive of a mixture of type II collagen with a certain amount of type I collagen. The NaDodSO4 polyacrylamide gel electrophoresis showed $\alpha 1$, $\alpha 2$, and β bands compatible with the presence of a mixture of types I and II collagens. The result of the transblot studies showed protein reactive against anti-type II collagen in the cochlear sample (Fig 1, panel B, lane 1), corresponding to $\alpha 1(II)$. The presence of type II collagen also is shown by immunoperoxidase studies (Fig 2).

Several types of collagens exist in connective tissues.[16] Only recently has sufficient knowledge of collagen biochemistry been developed to allow the

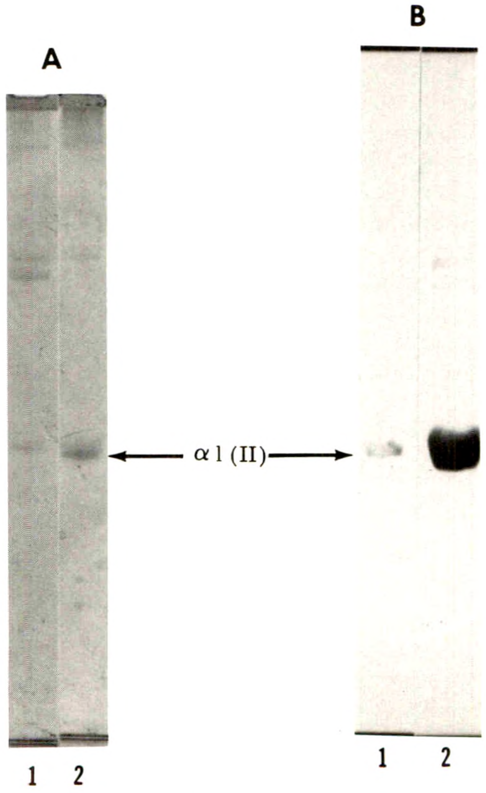

Fig 1. Transblot of guinea pig cochlea extract. Aliquots of extracted cochlear bone (50 μg), lane 1, and type II collagen (20 μg), lane 2, were analyzed with 5% NaDodSO4-PAGE. Gel set was transblotted onto nitrocellulose paper. Nitrocellulose paper was incubated with monoclonal anti-type II collagen antibody (1/1,000), conjugated with goat antimouse IgG peroxidase (1/2,000), and developed with horseradish peroxidase color development reagent. Panel A — Coomassie brilliant blue stain gel, panel B — transblot of gel set on panel A.

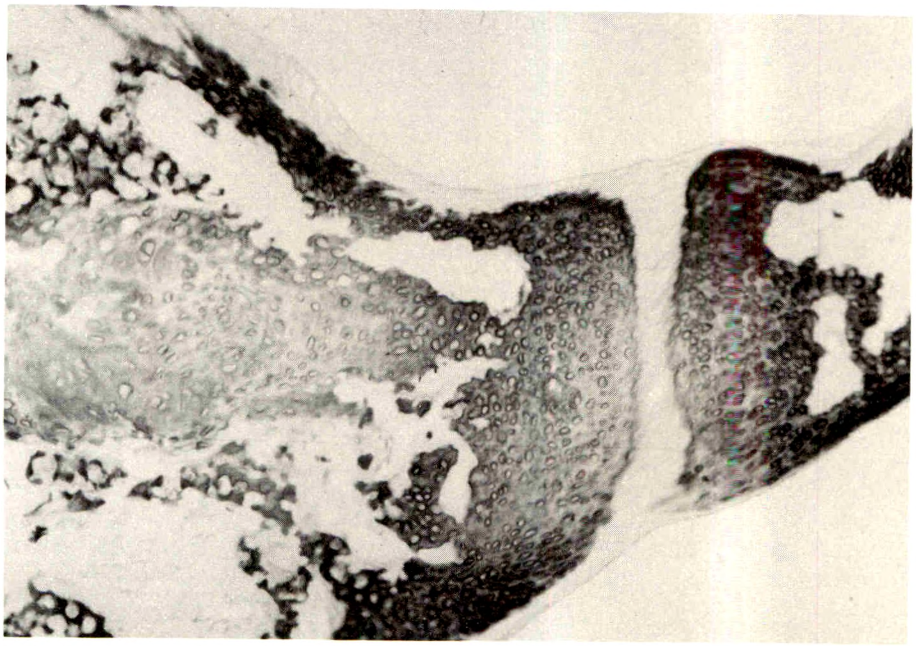

Fig 2. Stapediovestibular joint of human stapes and fissula ante fenestram showed positive immunoperoxidase staining (original x60). First antibody was mouse monoclonal antibody against bovine type II collagen, and second antibody was enzyme-labeled goat anti-mouse antibody. Dark color represents type II collagens.

identification and purification of at least 12 different types of collagen.[17] Although the basic structure of each type of collagen is similar, each type of collagen is antigenically distinctive.[16] Type I is the most predominant interstitial structural protein in all tissues except hyaline cartilage. Type II collagen is in cartilage tissues.

The collagens of the middle ear structure were studied previously by Birchall et al,[18] who showed by polyacrylamide electrophoresis that the major collagen found in human ossicles was type I collagen. Their study did not include the amino acid analysis of human ossicles, however. Using electrophoresis alone makes it difficult to differentiate between samples containing type I collagen and samples containing both type I and type II collagens. This study shows, however, that the stapes and cochlea contain both type I and type II collagens. The results are consistent with the immunoblot study as well as the immunofluorescence or immunoperoxidase study of these bones (Fig 2). We have demonstrated, by the immunofluorescence or immunoperoxidase method using monoclonal antibodies against type II collagen, that type II collagen exists in the ossicular joints and stapes footplate.[19] This immunohistologic study indicates the presence of type II collagen in the joint of human ossicles and the endochondral layer of the otic capsules. The exact quantity of type II collagen in this tissue has not been made clear by either study, as yet. A more definitive study would be a chemical isolation of type II collagen from this bony tissue extracted in large quantities. The implication of the presence of type II collagen in this tissue is very important, since we consider it an autoantigen responsible for the induction of autoimmune responses in otosclerosis in humans.

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AMERICAN AUDITORY SOCIETY

The 15th annual meeting of the American Auditory Society will be held in Boston on Thursday, November 17, 1988. The meeting is scheduled in conjunction with the annual meeting of the American Speech-Language-Hearing Association. For further information, contact Frank E. Musiek, PhD, Program Chairman, Dartmouth-Hitchcock Medical Center, 2 Maynard Street, Hanover, NH 03756.

Ann Otol Rhinol Laryngol 97:1988

STUDY OF HUMIDIFICATION POTENTIAL OF A HEAT AND MOISTURE EXCHANGER IN TRACHEOTOMIZED DOGS

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Though a heat and moisture exchanger (HME) has been used in clinical practice following a tracheotomy on a limited basis, no work has been done to document the humidification potential of an HME in this situation. Eighteen dogs underwent tracheotomy and were killed at either 1 day (nine dogs) or 10 days (nine dogs) postoperatively. Following the tracheotomy, the animals were divided into three groups according to the type of humidification received: ambient conditions, warm mist, or HME. The tracheal mucosa was studied for histologic changes in the cilia, the epithelium, submucosal reaction, and mucus production at the level of the carina. The results were significant ($p = .02$) for the interaction of the experimental type and method of treatment in their effect on the histologic changes noted at the carina. The study supports the use of an HME as an alternative for long-term humidification in a patient with a tracheotomy.

KEY WORDS — heat and moisture exchanger, humidification, tracheotomy.

In the normal physiologic state, the upper aerodigestive tract provides the necessary humidification and heating of inspired air. Mouth breathing alone results in air with a relative humidity of 62%, while nasal breathing alone provides a relative humidity of 70% at 37°C.[1] Maintenance of this humidification process is essential for normal mucociliary function in the tracheobronchial tree. If the relative humidity of the inspired gas falls below 70%, ciliary function diminishes within 15 minutes. Ciliary function ceases completely when the relative humidity falls below 30% to 50%.[2]

In patients who have undergone a tracheotomy, the ability to heat and humidify inspired air is lost. An artificial method of performing this function is necessary to maintain normal function of the tracheobronchial tree. Heated humidifiers have been used almost exclusively to provide heat and humidification for inspired gas. An alternative to this, a heat and moisture exchanger (HME), has been shown to be efficacious when attached to an endotracheal tube during assisted ventilation in an intensive care unit or during general anesthesia.[3,4]

This study was designed to evaluate the humidification potential of an HME following tracheotomy in an animal model. It was hypothesized that the HME would provide satisfactory humidification and that histologic examination of the trachea would confirm this fact.

MATERIALS AND METHODS

Eighteen dogs were procured from local kennels. The animals were 2- to 4-year-old adults with weights of approximately 20 kg. A veterinary examination was performed to assure the presence of good health; specificially, no animals were entered into the study if they showed evidence of upper or lower respiratory tract infection.

A tracheotomy was performed under sterile conditions in all animals through a horizontal skin incision. Acepromazine (0.55 mg/kg) was given subcutaneously prior to induction of general anesthesia with thiamylal sodium (17.6 mg/kg). Anesthesia was maintained with a balanced technique using methoxyflurane, nitrous oxide, and oxygen. Hemostasis was obtained with the electrocautery and chromic suture. A window of cartilage was removed from the trachea at approximately the level of the third tracheal ring. An appropriate size cuffed tracheotomy tube with an inner cannula was used in all animals. The tubes had inner diameters of 7, 8, and 9 mm.

Postoperatively, the tracheotomy tube was suctioned every 30 minutes and as often as necessary for the first hour, and then every 60 minutes and as often as necessary for the next 3 hours following the procedure. After that time, suctioning was performed every 4 hours and as often as necessary. This was performed in a clean but not sterile manner with the attendants washing their hands before performing each suctioning. Catheters were reused following cleaning with hydrogen peroxide, but each was used on only one animal. If the secretions were very thick, approximately 1 mL of normal sa-

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TABLE 1. HISTOLOGIC SCORES (MEAN ± SD) FOR TRACHEAL SECTIONS

Treatment	*Acute Changes*	*Chronic Changes*
No humidity	1.7 ± 0.6	3.0 ± 1.0
Tent	2.0 ± 1.7	6.0 ± 1.7
HME	3.3 ± 2.0	1.7 ± 1.5

Scores obtained by mathematic averaging of total histopathologic changes in cilia, epithelium, submucosal reaction, and secretory gland activity.

HME — heat and moisture exchanger.

line was instilled into the tracheotomy tube prior to suctioning.

The inner cannula was cleaned with hydrogen peroxide and pipe cleaners prior to rinsing with normal saline. After the excessive saline was shaken off, the inner cannula was replaced. This was performed at least every 2 hours and after each suctioning. The tracheotomy site was cleaned with diluted hydrogen peroxide every 4 hours and as needed. An antimicrobial ointment was applied to the tracheotomy site twice daily. The tracheotomy ties were checked every 8 hours for appropriate tightness.

The animals were under constant surveillance for signs of airway obstruction. In addition, the animals' necks were checked regularly for evidence of swelling, excessive crepitation, or bleeding. The animals did not require systemic antimicrobial therapy or analgesic therapy during the observation period. At the conclusion of the study, the animals were killed by an overdose of Socumb (Butler Co, Columbus, Ohio) administered intravenously in the dose of 0.22 mL/kg body weight. The trachea was obtained and prepared for histologic examination. In all animals, the tracheal mucosa that was examined was 1 cm proximal to the carina.

The dogs were divided into three groups containing six animals each. The animals in group 1 received no humidification following their tracheotomy. They were maintained in ambient conditions with a room temperature of 22°C ± 1°C and a relative humidity of 40% to 60%. Three animals (group 1A) were killed 1 day after tracheotomy, and three animals (group 1B) were killed 10 days after tracheotomy. Animals in group 2 had an HME (Trach-Vent, Gibeck Respiration, Upplands Vasby, Sweden) applied immediately after tracheotomy. Groups 2A and 2B were killed on the same schedule as the animals in group 1. Animals in group 3 received conventional humidification after tracheotomy. Warm mist (27°C to 35°C at 80% to 100% relative humidity) was delivered by a heated nebulizer into a standard mist tent covering the cage that housed the animal. The animals in group 3A were killed 1 day after tracheotomy, and the animals in group 3B were killed 10 days after tracheotomy.

TABLE 2. RELATIONSHIP BETWEEN TREATMENT GROUP AND HISTOLOGIC EFFECTS OF TRACHEOTOMY

Animal	*Cilia*	*Epithelium*	*Submucosa*	*Mucus Production*
Acute changes				
Group 1A (no humidity)				
1	+	+	0	0
2	+	+	0	0
3	+	0	0	0
Group 2A (tent)				
4	++	+	0	–
5	+	0	0	0
6	0	0	0	–
Group 3A (HME)				
7	0	0	0	–
8	+	0	++	–
9	+	+++	0	+
Chronic changes				
Group 1B (no humidity)				
10	+	+	++	0
11	+	0	+	0
12	+	+	+	0
Group 2B (tent)				
13	++	+++	+	–
14	+	+++	++	–
15	+	+	++	0
Group 3B (HME)				
16	+	+	0	0
17	+	+	0	+
18	0	0	0	0

See text for scoring.

After the animals were killed, the tracheal ring 1 cm above the carina was obtained and fixed in 10% buffered formalin. Histopathologic sections were stained with hematoxylin and eosin and periodic acid-Schiff (PAS) stain for mucus. The slides were

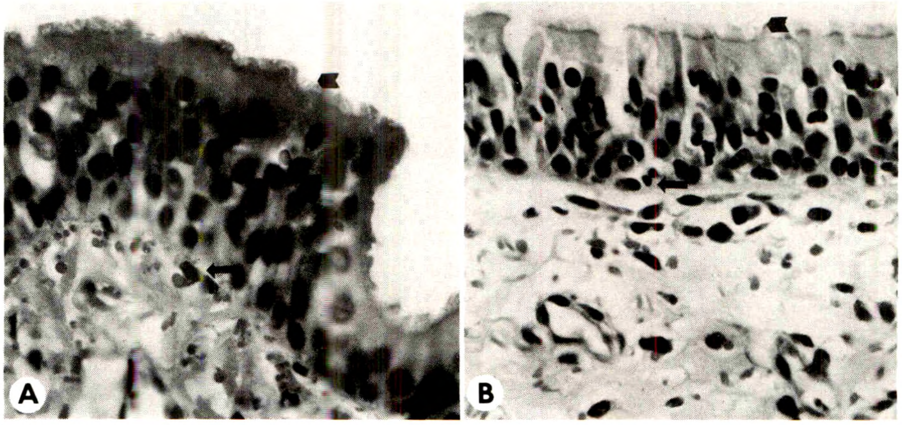

Fig 1. Histology of canine respiratory mucosa (H & E, original x63). Ciliary layer (arrowheads) and basement membrane (arrows) are indicated. A) Mucosa approximately 1 cm proximal to carina obtained 10 days after tracheotomy with subsequent use of HME. Minimal changes are seen. B) Normal mucosa.

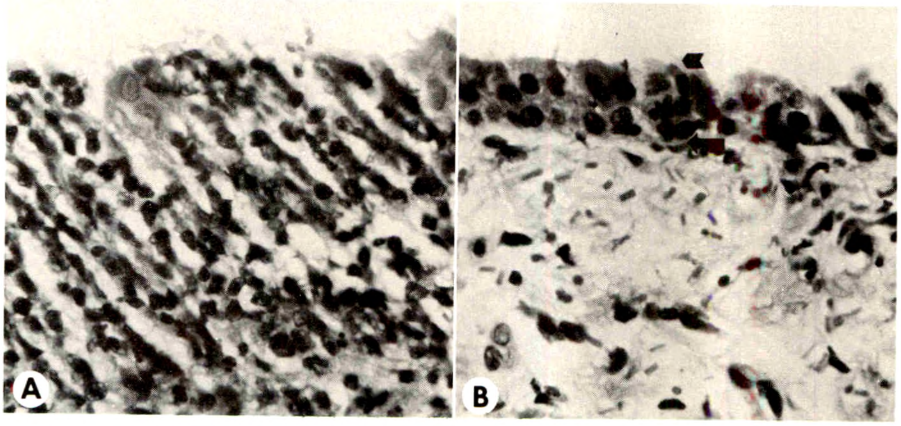

Fig 2. Mild to moderate inflammation of tracheal mucosa of tracheotomized dogs A) following 10 days in humidification tent and B) with no additional humidity (H & E, original x63). In A, there is no recognizable architecture. In B, ciliary layer (arrowhead) is markedly disrupted. Basement membrane is noted for orientation (arrow).

read with pathologic consultation without knowledge of animal or level of the slide. Using the method of Yoshpe et al,[5] changes in cilia, epithelium, submucosal reaction, and secretory gland activity were assessed qualitatively. One normal dog was killed and underwent histologic preparation for comparison. Even though wide variations in microscopic anatomy may be present in normal animals, it was deemed unnecessary to kill additional animals since the histologic findings fit the classic description as well as the results recently reported by Yoshpe et al.[5]

The following scale was used for evaluation[5]:

1. Cilia: 0, normal; +, patchy destruction $\leq 50\%$; ++, almost total destruction.
2. Epithelium: 0, normal; +, focal erosion; ++, marked erosion with underlying ulcerations; +++, squamous metaplasia.
3. Submucosa: 0, normal; +, edema; ++, edema and inflammatory cell infiltrate.
4. Mucus production (PAS stain): 0, normally active (comparable to the normal control); +, hyperactive (greater than the normal control); −, inactive (markedly less than the normal control).

RESULTS

The normal respiratory epithelium of dogs consists of ciliated pseudostratified columnar epithelium interspersed with mucous or goblet cells. The submucosa contains secretory glands in connective tissue overlying cartilage covered by perichondrium.

The effect of treatment (no humidity, tent, or HME) and experimental type (acute, chronic) on histologic score was determined by an analysis of variance for the tissue section obtained from the carina. A mean histologic score for each of the six subgroups was obtained by mathematic averaging of the total histopathologic changes in the cilia, the epithelium, submucosal reaction, and secretory gland activity. Though equality of variance between groups and the normality of data could not be tested adequately, both were assumed in this analysis.

There was no significant difference between the mean histologic scores for the sections obtained. However, there was found to be a significant interaction ($p = .02$) of the experimental type and the method of treatment in their effect on the histologic score of the tracheal mucosa (Table 1). As can be seen from Table 2, the relationship between the treatment group and the histologic score differed depending on the type of experiment. In the two treatment groups with no added humidity or tent, those animals in the chronic group had higher histologic scores. In contrast, the animals in the chronic group with HME had lower histologic scores.

DISCUSSION

On the basis of the data presented, the HME appears to have a protective effect on the tracheal mucosa following tracheotomy when used over a prolonged period of time. In the other two treatment groups, however, histopathologic changes in the distal trachea appeared to increase over the first 10 days following tracheotomy. This contrasted with the HME group, in which there was a return to normal in the first 10 days following tracheotomy.

The HME has been in clinical use for a number of years, specificially in patients requiring endotracheal intubation for either general anesthesia or assisted ventilation. Though its clinical success is unquestioned in that population, acceptance in the United States for patients with tracheotomies has been slow. No prior studies have investigated the effect of this device on the mucosal lining of the tracheobronchial tree. As demonstrated in Fig 1A, a section of respiratory mucosa taken from a dog following a tracheotomy with the use of an HME for 10 days is very similar histologically to a dog's normal respiratory mucosa (Fig 1B). In comparison, mild to moderate inflammation characterizes the tracheal mucosa of a dog that was placed in a humidification tent following tracheotomy (Fig 2A) or given no additional humidity (Fig 2B).

The findings in this study support the HME as an alternative means of humidification in patients following tracheotomy.

ACKNOWLEDGMENT — The authors thank Paula Klusman for her expert assistance and advice in the care of the animals used in this study.

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VI INTERNATIONAL SYMPOSIUM ON THE FACIAL NERVE

The VI International Symposium on the Facial Nerve will be held October 2-5, 1988, in Rio de Janeiro. For further information, contact Secretariat, Congrex, c/o Decio Castro, MD, Rua do Ouvidor 60, Suite 705, 20040 Rio de Janeiro, RJ, Brazil.

Ann Otol Rhinol Laryngol 97:1988

IMAGING CASE STUDY OF THE MONTH

ENLARGED JUGULAR FORAMEN

DONALD P. MUELLER, MD

KENNETH D. DOLAN, MD

IOWA CITY, IOWA

PATIENT

A 57-year-old woman presented with a red mass medial to the right tympanic membrane observed by her otolaryngologist to be enlarging. During follow-up, serial audiometric examinations demonstrated a 15-dB conductive hearing loss. On admission to our institution, the patient noted pulsatile tinnitus and aural fullness in the right ear. On physical examination, Weber's test lateralized to the right. The mass was identified in the anterior-inferior quadrant, was nonmobile, and did not blanch with positive pressure. The remainder of the tympanic membrane was mobile. No objective tinnitus was noted on auscultation with Toynbee's otoscope.

RADIOGRAPHIC FINDINGS

Coronal examination of the temporal bones was performed at the referring institution. An anterior view revealed a soft tissue mass over the promontory extending into the hypotympanum. Focal erosion of the carotid plate was present (Fig 1A). Enlargement of the jugular canal was present on a more posterior view (Fig 1B). Angiographic study demonstrated a 2.5-cm enhanced area in the jugular bulb thought to represent a glomus jugulare tumor.

SURGICAL FINDINGS

Mastoidectomy and exploratory surgery were performed with a working diagnosis of a glomus jugulare tumor extending into the middle ear. The jugular bone cover was found to be intact, and the middle ear mass was a glomus tympanicum lesion that extended forward into the hypotympanum–eustachian tube area. The glomus tympanicum mass was removed.

DISCUSSION

This case is presented as an example of two unrelated entities in combination that had a misleading appearance on computed tomography.

An enlarged jugular bulb is not uncommon. In an autopsy review, Rhoton and Buza[1] demonstrated the right foramen to be larger than the left in 68% of cases. Overton and Ritter[2] confirmed that a large jugular bulb may extend into the hypotympanum or mesotympanum.

There is no relationship, to our knowledge, between the large jugular bulb and the glomus tympanicum lesion. However, a large jugular vein, a glomus jugulare tumor, and a glomus tympanicum tumor may simulate one another as a red mass medial to the tympanic membrane.

The glomus jugulare tumor is initially silent, and symptoms may not develop until there is extension into the middle ear cavity.[3] Otoscopically, it may be visualized as a reddish purple mass. Studies of the

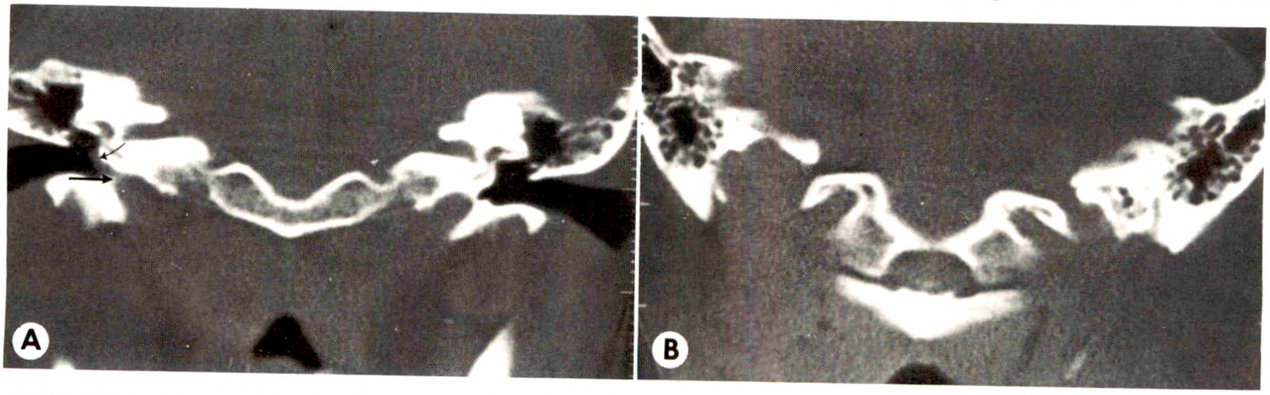

Fig 1. Coronal computed tomograph at bone window. A) Focal bony erosion (straight arrow) and soft tissue density in hypotympanum (curved arrow). B) Image slightly posterior to A showing enlargement of jugular fossa.

From the Department of Radiology, University of Iowa Hospitals and Clinics, Iowa City.

REPRINTS — Kenneth D. Dolan, MD, Dept of Radiology, University of Iowa Hospitals and Clinics, Iowa City, IA 52242.

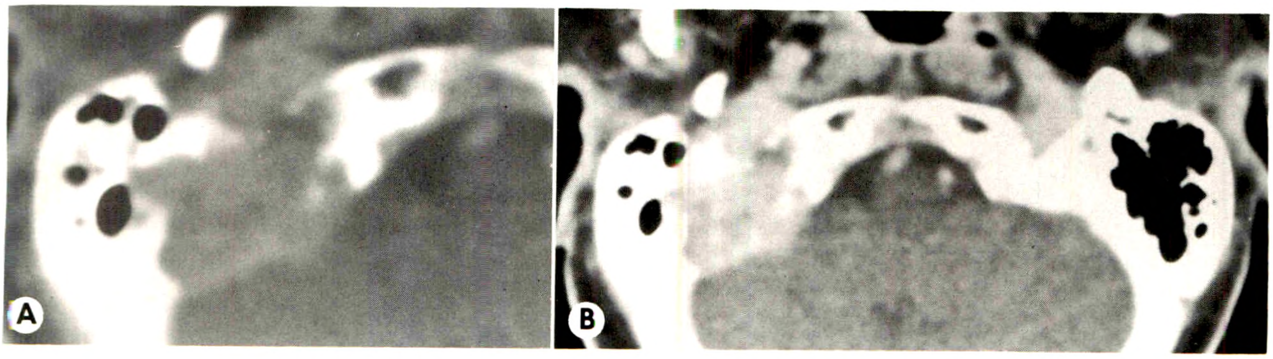

Fig 2. Axial computed tomograph of glomus jugulare tumor photographed A) at bone window, illustrating irregular, "moth-eaten" enlargement of jugular fossa, and B) at soft tissue window, demonstrating intense enhancement.

jugular fossa are characterized by erosion of the cortical outline.[4] Chakeres and LeMasters[5] have reviewed the CT findings associated with temporal bone paragangliomas. Findings included early destruction of the bony plates separating the hypotympanum from the jugular fossa, with a soft tissue mass protruding from the jugular fossa into the middle ear cavity. Progressive circular enlargement of the jugular fossa with a "moth-eaten" permeative pattern of destruction was demonstrated (Fig 2A). Erosion of the caroticojugular spine and thinning of the jugular tubercle also were demonstrated. Large paragangliomas uniformly demonstrated more contrast enhancement than surrounding parapharyngeal musculature or brain parenchyma (Fig 2B).

Glomus tympanicum lesions usually arise over the cochlear promontory and are related to the cochlear neural plexus. They are not associated with erosion of the jugular canal, but may produce focal erosion adjacent to the mass as seen in our patient (Fig 1A). They may produce a large mass that essentially fills the mesotympanum and hypotympanum.

The large jugular bulb is a particular problem in childhood, when thinning of the jugular bone surface allows the examiner to see the underlying vein through the tympanic membrane.[6] This usually occurs well below the usual age range for glomus tumors.

Our purpose in presenting this case is to illustrate the diagnostic quandary produced by the coincidental occurrence of a large jugular bulb and a glomus tympanicum lesion.

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Ann Otol Rhinol Laryngol 97:1988

PATHOLOGY CONSULTATION

ALVEOLAR SOFT-PART SARCOMA

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HOUSTON, TEXAS

Approximately 25% of all alveolar soft-part sarcomas have their origin in the head, where the tongue and orbit are sites of predilection. The neoplasms possess characteristic light and electron-optic features, yet their histogenesis remains unclear. Recurrences, early metastases, and lethality over a prolonged period are pertinent biologic findings.

Alveolar soft-part sarcoma is an uncommon and histogenetically enigmatic malignancy with a predilection for the extremities. Approximately 25% of the neoplasms take origin in the head and neck, where the tongue and orbit are favored sites (see Table).[1-5] Presenting over a wide age range, alveolar soft-part sarcomas are found most often in adolescents and young adults between 15 and 35 years of age.[1]

In gross appearance, the neoplasm is usually well vascularized and circumscribed, but unencapsulated. The light-optic characteristics are distinctive and nearly pathognomonic. An organoid or pseudoalveolar pattern, accentuated by reticulin stains, is imparted by nests of cells separated by thin fibrous septa with thin vascular channels (Fig 1). The neoplastic cells are large and round to polyhedral with distinct cell borders. The nuclei often contain a single and prominent nucleolus and are paracentral or eccentric in position. Binucleate forms can be seen occasionally. Mitoses are never numerous. Although basically acidophilic, the cytoplasm varies from granular to reticulated and even vacuolated. Found with variable degrees of success in the cytoplasm are PAS-positive, diastase-resistant crystalline structures, which probably result from a coalescence of peculiar membrane-bound, acid phosphatase–positive granules. With electron-optic examination, a prominent Golgi complex is usually present, and distinctively, numerous electron-dense membrane-bound organelles of variable size, shape, and electron density are in the cytoplasm. Among the latter are rhomboids with a crystalline substructure and a periodicity between 5 and 10 nm. They vary in size and shape (Fig 2).

ALVEOLAR SOFT-PART SARCOMA IN HEAD AND NECK

Primary Site	*No. of Cases*	*Percent*
Tongue	23	47.7
Orbit	17	35.2
Buccal mucosa	3	6.0
Floor of mouth	2	4.5
Temporal-parotid-masseteric area	2	4.6
Infratemporal fossa	1	2.0
Total	48	100.0

Despite rather intensive study, the alveolar soft-part sarcoma has resisted histogenetic definition. Two principal theories of origin prevail: 1) neural crest, particularly Schwann cell and paraganglia, and 2) myogenic. Proponents of both hypotheses have relied primarily on electron-optic observations.[6-9] With the advent of immunocytochemistry, the myogenic theory has become more plausible. Nonimmunoreactivity with neurone-specific enolase and S-100 protein antigen and an inability to obtain formaldehyde-induced fluorescence seriously detract from a neural crest origin.[9] On the other hand, Mukai and associates[10-12] continue to build a strong case for myogenic origin and in particular for rhabdomyoblastic differentiation (actin, desmin, Z-protein and B-enolase immunoreactivity). They further conclude that the characteristic crystalloids consist of substances making up the Z-band of muscle. Their findings further place the proposition that the neoplasm is an "angioreninoma" in considerable doubt.[13]

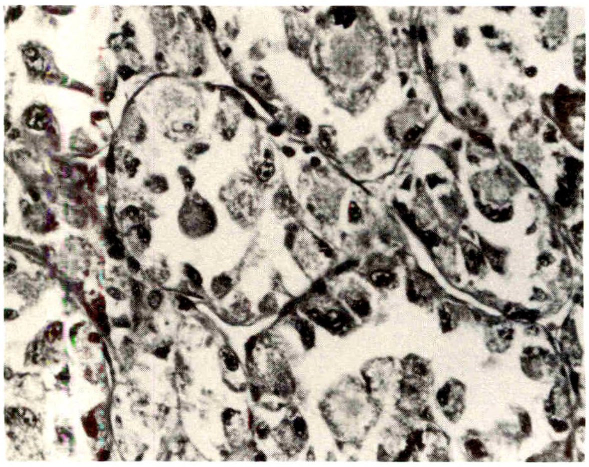

Fig 1. Alveolar soft-part sarcoma from base of tongue of 19-month-old girl (H & E, original x420). Note organoid arrangement and variable size of neoplastic cells.

From the University of Texas M. D. Anderson Hospital and Tumor Institute at Houston.

REPRINTS — John G. Batsakis, MD, Division of Pathology, M. D. Anderson Hospital, Texas Medical Center, Houston, TX 77030.

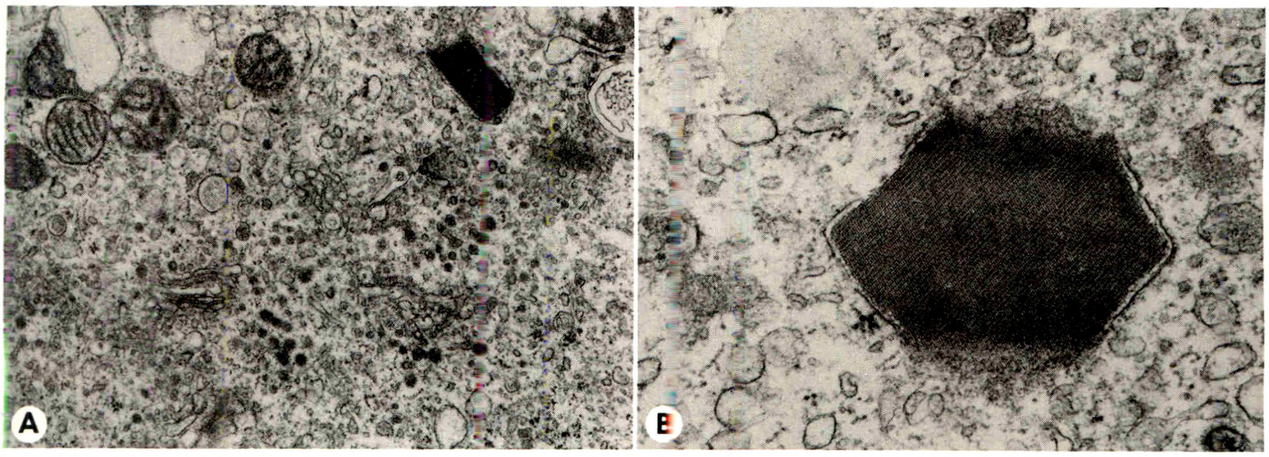

Fig 2. Electron micrographs of alveolar soft-part sarcoma of base of tongue. A) Cytoplasm is rich in organelles, including characteristic crystal in upper right quadrant (original x34,500). B) Higher power electron-optic view of characteristic rhomboid-shaped crystal in cytoplasm (original x76,000). Crystal is composed of laminar filaments arranged in lattice pattern.

The malignancy of an alveolar soft-part sarcoma is unquestioned. For a purportedly slow-growing neoplasm, however, there is a disproportionate frequency of distant metastases early in the course of the disease. Of 36 patients reviewed by Enzinger and Weiss,[1] 13 had demonstrable metastases before the primary was detected. In other patients, the metastases may be delayed for years. The lungs are involved in all patients with distant metastases. The brain and skeleton follow in frequency. Metastases to lymph nodes are not common. Cerebral involvement is said to be found more often with alveolar soft-part sarcoma than with any other soft-tissue sarcoma.[1]

Lieberman et al[14] indicate that for alveolar soft-part sarcoma at all sites, the 2-, 5-, and 10-year survivals are 83%, 59%, and 47%, respectively. Evans's[5] data coincide with his patients, having a median survival of 79 months. Ten of 23 patients with nonorbital head and neck alveolar soft-part sarcomas and with a recorded follow-up have died of their malignancies, eight of the ten within 5 years after primary treatment.[2,3,5] Data from orbital primaries suggest that this site may have a more favorable outlook.[4] The possibility of an amelioration of lethality in infants and young children cannot be confirmed for head and neck alveolar soft-part sarcomas.

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LETTERS TO THE EDITOR

To the Editor:

I agree with Dr Y. Finkelstein et al (Eliminating the Toynbee Phenomenon in Patients with Nasal Packs. *Ann Otol Rhinol Laryngol* 1988;97:74-7) that one should attempt to eliminate the Toynbee phenomenon in patients with nasal packs.

I have found a short length of plastic drinking straw to work better than a length of gastric tube or Nelaton. Vernon Gray, MD, formerly of Los Angeles, described this improvement in nasal dressing (personal communication). The straw is cut so that the corrugated portion rests on the floor of the nasal vestibule. A 1.25-cm (½ in) gauze strip impregnated with an antibiotic ointment holds the straw in place, and a physiologic internal nasal dressing is thus obtained.

I believe in internal nasal dressing, and this innovation has made it very tolerable to my patients over the years.

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To the Editor:

I read with interest the article by Dr Nussbaum et al (Hypodermic Needles: An Unusual Tracheobronchial Foreign Body, *Ann Otol Rhinol Laryngol* 1987;96:698-700). They stated that in their literature review covering almost 4,000 cases, no series mentioned hypodermic needles as a foreign body. They alerted us to this possibility in intravenous drug abusers. I wish to add my experience to theirs.

The following incident occurred in 1982 when I was rotating as an intern in the intensive care unit at the US Naval Hospital in Portsmouth, Virginia. While reviewing the daily chest films, I noted that a large bore hypodermic needle appeared to be lying in the trachea of a patient hospitalized for acute decompensation of chronic lung disease. It was felt initially to be outside the chest, and a diligent but unsuccessful search was made. Another film was taken and again showed a needle in the same location. While a second search was being made, the patient, who then was undergoing suction via the endotracheal tube, coughed the 18-gauge needle out through the tube onto his chest. What apparently had happened was that a nurse had instilled a few milliliters of saline to facilitate suctioning using a syringe with needle (loosely) attached. When the nurse forcibly discharged the syringe, the needle also entered the tube, unnoticed.

It is unknown how often this happens and goes unreported. Indeed, it may happen more often at training institutions. Medical and nursing faculty should be alerted to this possibility and thus to its prevention.

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BOOK REVIEWS

Nose, Throat and Ears

I. Friedmann, ed; M. H. Bennett, F. Piris, contributors. *Systemic Pathology*, W. St. C. Symmers, series ed. 3rd ed. Hard cover, illustrated, indexed, 359 pages, 1986. Churchill Livingstone, Inc, London, $85.

This volume has been dedicated to the diseases of the head and neck, particularly the nose, throat, nasopharynx, tonsils, and ears, because of the increasing clinicopathologic specialization in this area and the importance of recognizing the histopathologic features of selected neoplastic and nonneoplastic conditions that are common to and/or peculiar to the upper respiratory tract and ear. Previously, these topics were distributed throughout several volumes of the second edition of *Systemic Pathology*, and even then were presented in an incomplete and abbreviated manner. The present volume was intended not only for the pathologist with interest in this area, but also for the otolaryngologist, for whom it would provide a sound basis for diagnosis and research, together with an appreciation of the difficulties in making tissue diagnosis from the inherently small samples obtained and the potential for artifactual traumatic distortion.

The book is divided into five parts: 1) nose and paranasal sinuses, 2) nasopharynx, 3) tonsils and oropharynx, 4) larynx, and 5) ear. Each part has chapters on anatomy and histology, and each part has separate segments that deal directly with infectious and noninfectious inflammatory conditions and neoplastic and nonneoplastic diseases. Each chapter begins with a brief outline and ends with a very complete bibliography. The authors provide interesting historical vignettes when appropriate. It is written in a clear, authoritative, and enjoyable style. Controversial topics involving differences in tumor classification and disease nomenclature are recognized, debated, and resolved, although the resolutions are not always in concert with current US texts.

The paper and printed format are of the highest quality. The double columned chapters are clearly defined by bold highlighted titles and subtitles. The index covers the subject matter completely. One of the most outstanding features is the exceptional quality and choice of illustrations; they are large, clear, and representative of the disease entities they portray. The electron micrographs are also quite remarkable.

As would be expected, there is an appropriate increase in the discussion of those diseases that are common to or even quite particular to the head and neck. Increased detail is given to such infectious diseases as rhinoscleroma, rhinosporidiosis, and leishmaniasis. Fairly recently described entities such as myospherulosis are presented. Single chapters are dedicated to important differential diagnoses such as that of the nonhealing nasal granulomas of unknown cause (eg, midfacial destructive lesions). Particular neoplastic lesions such as olfactory neuroblastoma, nasopharyngeal carcinoma, and others are clearly emphasized. Nonneoplastic maladies of the inner ear, including otosclerosis and Meniere's disease, are well illustrated and discussed both in pathologic and clinical terms.

Finally, as would be suggested by the sequence in the title (that is, NTE rather than the conventional US abbreviation ENT), there are differences in nomenclature, tumor classification, and stated malignant potential in certain diseases. The Stewart type of midline granuloma (midline malignant reticulosis) is considered to be a nonneoplastic necrotizing granuloma, while the tendency in the United States is to view this lesion as a malignant lymphoproliferative disorder (neoplastic condition) closely related to lymphoma. Transitional papilloma is the preferred term in this text over sinonasal papillomas including inverted papilloma; the so-called cylindrical cell papilloma is not considered to be a member of the sinonasal papilloma group and is classified as microcystic papillary adenoma.

This is an impressive text on the histopathology of the upper respiratory tract and ear, well illustrated and clearly written, and is well worth the investment as a reference for the otolaryngologist and the general pathologist. The excellent illustrations serving as an atlas of pathology almost justify the cost alone.

Col James C. Durham, DDS, MD
Washington, DC

Anatomy of the Temporal Bone With Surgical Implications

Harold F. Schuknecht and A. Julianna Gulya. Hard cover, illustrated, indexed, 350 pages, 1986. Lea & Febiger, Philadelphia, $125.

An understanding of the pathology and anatomy involved in a disease process must be acquired for progress to be made in allaying it. Toward this end, Schuknecht has made good use of the collection of temporal bones that is at his disposal. In 1974, he superbly presented the pathologic basis of ear disease in *Pathology of the Ear*. Now, he and Gulya have taken another step in the process of understanding the fundamentals of ear disease by presenting the normal anatomy, and variations in it of the structures involved.

Perhaps this text does not fill as large a void as did the unique text on pathology of the ear. Nevertheless, it is certainly a significant augmentation to the other books on normal and variant anatomy of the ear. The format used in the chapter on phylogeny and embryology is helpful in explaining the complexities of embryonic development, presenting it in structural-change sequences as well as time-lapse sequences. There are other worthwhile contributions, especially in surgical application of the knowledge of oto-anatomy. Examples include the basic shapes of the ossicles, which are important in prosthesis attachment; photographic illustrations of variant anatomy, especially where dehiscence of the facial nerve occurs; functional reasons for severing the tensor tympani muscle when repairing a large perforation by myringoplasty; and a study of tract pneumatization in the temporal bone.

The most obvious way in which this book surpasses similar works is the visual aid that accompanies two of its chapters. Although the otolaryngologist with advanced training in otology or otoneurology may not benefit as much from this additional feature as the less-experienced reader, the advantage of having three-dimensional illustrations available to accompany a text is unquestionable.

The contributions of the more conventional illustrations (temporal bone sections) that accompany this text are not overshadowed by the three-dimensional ones, for they are consistent tours de force that substantially embellish the text. Indeed, the clinician experienced in otology can learn a great deal from just the illustrations, unaccompanied by the text.

The text and the illustrations of temporal bone sections conjoin to give an extraordinarily vivid impression of conventional ear anatomy, as well as otoneurologic and vascular anatomy. The success of this work lies in its role as a defining adjunct to other previously published texts on the anatomy of the ear.

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W. Corway, MD
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Plastic Reconstruction in the Head and Neck

T. R. Bull and Eugene Myers, eds. Hard cover illustrated, indexed, 214 pages, 1986. Butterworth & Co, London, $49.95.

This textbook covers selected topics of otolaryngologic reconstructive surgery and discusses their clinical management. The authors have compiled an extensive collection of specific head and neck reconstruction dilemmas and allowed their contributors to inform readers of what can be considered the state-of-the-art techniques. The authors have written this book for those with particular interests in the plastic and reconstructive aspects of head and neck surgery. It is also a good volume for those in general otolaryngology practice who must deal with patients with plastic and reconstructive problems. The book is divided into nine chapters and has 16 contributors.

The chapters dealing with rehabilitation of the voice and airway after vocal cord paralysis by Lavertu and Tucker are particularly informative and explicit. Techniques for both open and endoscopic vocal cord lateralization are well covered. Their reviews and illustrations of these techniques are excellent and provide a very well-indexed bibliography of this subject. Fisch and Mattox likewise provide the reader with a definitive treatment of subtotal temporal bone resection and facial rehabilitation for malignant tumors of the retromandibular fossa. They describe their principles for rerouting and/or grafting of the facial nerve. Plastic surgery of the nose is well covered in the volume. T. R. Bull describes the present status of rhinoplasty with many points covering instrumentation, the role of the septum, revision rhinoplasty, and complications. The subject of a logical and systematic approach to nasal fixation is described by Brain. This chapter is well written and illustrated. The subject of implant material for nasal reconstruction is also well covered and referenced. Mahe's chapter on management of the balding scalp is quite extensive and delves into many reconstructive techniques that can be used in the treatment of alopecia. The clinical assessment, histologic diagnosis, and anatomic variations are addressed.

The conclusions of this book are based on the extensive clinical experience of the particular authors. The data presented represent the successful use of these techniques in multitudes of patients. The bibliographies for each chapter are quite extensive and provide the reader with a significant source to investigate these topics further. The chapters are concise, yet extensive. The material is well organized and very readable.

The book provides an excellent sampling of several specific topics in plastic and reconstructive head and neck surgery and will be appreciated by those individuals who delve into this type of surgery.

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Emergencies in Otolaryngology

James Y. Suen and Stephen J. Wetmore. Soft cover, illustrated, indexed, 261 pages, 1986. Churchill Livingstone, New York, $30.

This softbound textbook is intended to be used as a guide for any physician involved in the initial evaluation of patients presenting otolaryngologic–head and neck problems. It is a collection of emergency situations loosely assembled into chapter groupings, including trauma (four chapters) and infection (three chapters). Intermingled among these groupings are disorders of the major anatomic regions and sites of the head and neck.

The scope of the disorders is extensive, with nearly 200 entities presented in an organized manner. Although an outline format is used, most of the authors include sections on cause, diagnosis, treatment, and differential diagnosis. Indeed, the depth of coverage is surprisingly greater than would be anticipated given the broad topic and the format employed. Photographs, x-ray films, and simple yet explicit diagrams are plentiful and serve to clarify important points in the text. The references to support epidemiologic, diagnostic, and therapeutic claims are current but limited.

There are, of course, limitations inherent in presenting such an extensive topic in an outline form. A balanced discussion of controversial areas is precluded. Redundancies occur; for example, the discussion of tuning fork testing principles is found in three separate chapters, two of which have the same instructive diagram. Such redundancies are apparent when the book is read from cover to cover, but are not likely to be evident when it is used as a diagnostic/therapeutic reference.

It is difficult to identify the shortcomings of this work, since it is overall one of the best publications in its class. For any physician who may encounter otolaryngologic emergencies, it should prove to be a valuable resource. Furthermore, it would serve to introduce new otolaryngology house staff members to the emergencies that they will eventually have to manage during their training years.

Robert P. Zitsch, MD
Dennis G. Pappas, MD
Birmingham, Alabama

Ear

John C. Ballantyne and Andrew Morrison, eds. 4th ed. *Rob & Smith's Operative Surgery*. Hugh Dudley, David C. Carter, and R. C. G. Russell, series eds. Hard cover, illustrated, indexed, 232 pages, 1986. Butterworths, London, £60.

Although many of the contributors to this atlas of ear surgery are Americans, its main distribution may be in Europe. The fact that this is the fourth edition is testimony to its popularity on both continents.

Every aspect of ear surgery is addressed, to some extent, including options in the surgical management of attic disease. Although the major portion of this text is devoted to cholesteatoma surgery, also included are surgical techniques not frequently addressed in other atlases, such as exposure of the sinus tympani through removal of bone anterior to the facial nerve in its vertical portion, removal of the pyramidal process, and approaching the sinus medial to the facial nerve through retrofacial cells. Another well-described technique is exposure of the attic to the extent of the posterior opening of the eustachian tube. According to the author, better aeration of the mastoid is achieved using this method. It must be emphasized that the potential hazards associated with these techniques should be considered carefully. Certainly, before clinical use, they should be practiced many times in a temporal bone laboratory.

In a systematic manner, the editors present surgical options in 26 well-organized chapters that are divided into three sections: external ear, middle ear and mastoid, and otoneurosurgery. Discussion of techniques in simple myringoplasty and tympanoplasty is scant; uses of autograft and homograft materials are described for ossicular chain reconstructions. The reader must be cautioned, however, that the contributions to this text represent individual techniques. For this reason, the conscientious surgeon will want to consult similar publications to acquire a menu of surgical options.

The otolaryngologist will find many useful points in this informative book; however, the treasure of this work is the ease with which the illustrations can be followed. The 14 contributing medical artists present broad coverage of this topic with illustrations that are neither too simplistic nor too overloaded. It is a remarkable assemblage of surgical procedures for the ear and is a significant supplement to other atlases on ear surgery.

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Clinical Measurement of Speech and Voice

R. J. Baken. Soft cover, illustrated, indexed, 518 pages, 1987. College-Hill Press. Boston, $35.

This book is intended for medical and rehabilitative professionals who assess and treat voice and speech disorders, but it is written primarily for speech pathologists, with whom rehabilitative responsibility usually resides. The title is slightly misleading, because the book is about machines: how instrumentation can be used to measure characteristics of the speech signal and the various physiologic events that produce it.

The book does not describe the usual clinical tasks with emphasis on auditory perceptual judgments made by the clinician. It postulates, instead, that listening is not enough, and that observation and measurement of the speech signal and its physiologic correlates offer significant advantages over unaided perceptual judgment. The author points out that biology and physics are having increased impact as knowledge of speech and language processes advances. Today, instruments are less costly and easier to use than previously, and they permit accurate, reliable real-time measurements that can improve therapeutic efficacy and efficiency.

Although the book is certainly on the cutting edge of technologic application, the instrumentation described comes from the professional literature and is not hypothetical or untried. Sophisticated clinicians may be able to adapt the instrumentation described in the book in creative, unique ways because of the inclusion of equipment function and underlying rationales. Some clinicians may conclude this book is too scientific, but scientists will find it clinically oriented, with many scientific details omitted that are important to them. The book breaks new ground in presenting a unified source of state-of-the-art instrumentation for evaluation and treatment of voice and speech disorders.

There are 11 chapters, beginning with an introduction and the fundamentals of electronics. Chapter 3 explains general purpose tools such as amplifiers, microphones, tape recorders, oscilloscopes, and chart recorders. Chapter 4 explains intensity and the various instruments used to measure it in speech. Chapter 5 focuses on frequency, with emphasis on instruments used in measuring the fundamental frequency of the voice. Chapters 4 and 5, respectively, contain thorough discussions of amplitude and frequency perturbation, or shimmer and jitter. Chapter 6 is concerned with the visualization and measurement of laryngeal function. Chapters 7 and 8 detail the measurement of air pressure, airflow, and volume. Chapter 9 contains a lengthy presentation of sound spectrography including basic principles; old and new instruments for measurement; a discussion of vowels, consonants, and voice onset time; and spectrographic categories of hoarseness. Chapter 10 encompasses measurement of velopharyngeal function including visualization; acoustic, airflow, and pressure measurements; and photoelectric detection of velar movement. Chapter 12 focuses on measurement of speech and chest wall movements through electromyographs, palatometry, and various transduction systems.

Baken has used over 300 figures and tables throughout the book to clarify the instruments and their principles of usage. Many figures are photographs of equipment, while many of the tables provide basic information needed to interpret data obtained through use of the instruments. Baken has organized the presentation of equipment in a logical manner, but some equipment can be used in many different ways. Therefore, readers should use the book's subject index to locate specific information if it is not found in the first chapter selected.

Baken assumes that readers have knowledge of speech pathology, mechanisms of speech production, assessment procedures, and treatment methodologies. For such readers, the book will serve as a compendium of currently available instrumentation, with applications and rationale. Unlike other books that merely list equipment and provide data, this book ties speech science to clinical assessment and should aid clinicians in the diagnosis of speech and voice disorders.

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INSTRUCTIONS TO AUTHORS

Send manuscripts to Editor Brian F. McCabe, MD, Department of Otolaryngology-Head and Neck Surgery, University of Iowa Hospitals, Iowa City, IA 52242. Original manuscripts dealing with clinical and scientific aspects of otolaryngology, bronchoesophagology, head and neck, maxillofacial and plastic surgery, audiology, speech pathology, and related specialties will be considered for publication.

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